Dental stem cells in tooth repair: A systematic review [version 1; peer review: 2 approved with reservations]

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Abstract

**Background:** Dental stem cells (DSCs) are self-renewable teeth cells, which help maintain or develop oral tissues. These cells can differentiate into odontoblasts, adipocytes, cementoblast-like cells, osteoblasts, or chondroblasts and form dentin/pulp. This systematic review aimed to summarize the current evidence regarding the role of these cells in dental pulp regeneration.

**Methods:** We searched the following databases: PubMed, Cochrane Library, MEDLINE, SCOPUS, ScienceDirect, and Web of Science using relevant keywords. Case reports and non-English studies were excluded. We included all studies using dental stem cells in tooth repair whether in vivo or in vitro studies.

**Results:** Dental pulp stem cell (DPSCs) is the most common type of cell. Most stem cells are incorporated and implanted into the root canals in different scaffold forms. Some experiments combine growth factors such as TDM, BMP, and G-CSF with stem cells to improve the results. The transplant of DPSCs and stem cells from apical papilla (SCAPs) was found to be associated with pulp-like recovery, efficient revascularization, enhanced chondrogenesis, and direct vascular supply of regenerated tissue.

**Conclusion:** The current evidence suggests that DPSCs, stem cells from human exfoliated deciduous teeth, and SCAPs are capable of providing sufficient pulp regeneration and vascularization. For the development of the dental repair field, it is important to screen for more effective stem cells, dentine releasing therapies, good biomimicry scaffolds, and good histological markers.

**Keywords**
tooth repair, dental stem cell, pulp regeneration, SCAPs, SHEDs
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Introduction
Regenerative dentistry is designed to recover dental anatomy and function. Regenerative endodontics procedures (REPs) of a damaged tooth are a series of biological processes aimed to restore the dental pulp’s physiological functions, cure periapical lesions, and substitute pulp-dentin complex cells and dentin. Three components are involved in these techniques: stem cells, growth and bio-materials, which are often known as scaffolds or templates.

The dental pulp consists of nerves, blood vessels and connective tissue to maintain teeth’s integrity. The nerves of the pulp can mediate pain, blood flow control, recruit immunocompetent cells, and act as a mesenchymal stem cells (MSCs) niche. Loss of tooth pulp stops the development of permanent root teeth that can weaken the periodontal connection and lead to teeth loss. Recent animal studies indicate that vascular dental pulp can be regenerated by cell-based therapy.

Dental stem cells (DSCs) are self-renewable teeth cells, which help maintain or develop oral tissues. In the literature, there are various types of adult dental cells, such as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells or stem cells of the developing root apical papilla (SCAPs), dental follicle stem cells (DFSCs), and dental MSCs (DMSCs). Such cells can differentiate into dentine/pulp, odontoblast, adipoocyte, cementblast-like, osteoblast, and chondroblast cells. DSC regenerative potential is explained through both natural and experimental conditions. Differentiated dentinoblasts, also called secondary odontoblasts, produce new dentine in response to dental cell injury. This regenerative process is called reparative tertiary dentinogenesis. This process of dentinogenesis was suggested to be used in the recruitment of endogenous DSCs. Most recent animal studies have investigated the role of DSCs in the regeneration of dental pulp tissues.

Bakhtiari et al. conducted a systematic review on 47 studies that investigate the role of stem cell therapy in regeneration of dentine-pulp complex; the current systematic review aimed to update this previous systematic review, presenting 57 articles, and summarizes the current evidence regarding the efficacy of dental stem cells in dental pulp regeneration in animal models.

Methods
We report this manuscript following the preferred reporting items systematic reviews and meta-analysis (PRISMA statement) guideline. All methods used in this review were conducted in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions.

Literature search strategy
We searched the following databases from January 2000 to June 2019: PubMed, Cochrane Library, MEDLINE, SCOPUS, ScienceDirect, and Web of Science using the following keywords: ((Dental pulp stem cells OR DPSCs OR stem cells OR human exfoliated deciduous teeth OR SHEDs OR Periodontal ligament stem cells OR developing root apical papilla OR SCAPs OR dental follicle stem cells OR DFSCs OR dental mesenchymal stem cells OR DMSCs) AND (pulp OR pulpal tissue OR pulp treatment OR pulpal therapy) AND (endodontic treatment OR deciduous teeth OR permanent teeth OR primary teeth OR dentition)) to identify the relevant studies.

Study selection process and eligibility criteria
Two authors screened the titles and abstracts of retrieved literature records. For titles and abstracts that deemed relevant to the research question, the full-text articles of these records were obtained and screened for eligibility according to the following criteria:

We included studies that meet the following PICOS criteria:
1) Population: Both in vitro and in vivo studies that investigate the endodontic regeneration following treatment with dental pulp stem cells.
2) Intervention/Comparator: studies that use all of the following types of stem cell in the regeneration of dental pulp tissue: DPSCs, SHEDs, SCAPs or DMSCs.
3) Outcomes: pulpal regeneration or repair.
4) Study design: All in vivo, in vitro, animal, or human studies.

We excluded all of the following studies: 1) Case reports and case series; and 2) non-English studies. In the case of multiple reports for the same study population, we analyzed data from the most updated dataset. Any discrepancies were resolved by discussion and consensus between reviewers.

Data extraction
Data extraction was performed manually and data were entered into a structured Microsoft Excel sheet (For Windows, Professional Plus version 2016). We extracted data of the following domains: 1) Characteristics of study design; 2) Baseline criteria of the included population; and 3) Study outcomes. There was not sufficient data for meta-analysis.

Results
Search strategy results
The electronic search retrieved 4433 unique articles. After removing duplications, 2780 articles were enrolled in the title/abstract screening. This led to the retrieval and screening of 327 full-text articles for eligibility. Studies that were not eligible with our criteria were excluded. In total 57 articles were included in the qualitative synthesis. A flow diagram of the selection process is shown in Figure 1. A summary of characteristics, models, and populations of the included studies and their key outcomes are shown in Table 1. Variation of the extracted data is reported in Table 2.

Types of stem cells
In this systematic review, we reviewed multiple types of stem cells, such as dental follicle stem cell (DFSC), bone marrow mesenchyme stem cell (BMSC), periodontal ligament stem cell (PDLSC), dental pulp extracellular matrix (DPEM), adipose-derived stem cell (ADSC), DPSC, SCAP, and SHED. The majority
of the studies (n=31; 46%) used DPSCs for regeneration of dentine-pulp complexes. Two out of eight studies, in which stem cells were transplanted into the renal capsule, used DPSCs. Moreover, DPSCs were used by 19 out of 40 studies on subcutaneous transplantation, three out of four studies on intra-canal transplantation, and two studies about allogeneic direct implantation into socket.

SCAP was reported in eight studies, six studies with subcutaneous implantation, and two studies on renal capsule transplantation. There are no experiments utilizing transplanted SCAP into root canal. DFSC is reported in six studies, five subcutaneous implantation studies, and one into-socket transplantation. Across four experiments that were all on subcutaneous transplants used SHEDs. Four experiments used BMSCs; two were transplanted to the renal capsule, one to the subcutaneous, and the other to the root canal. Three trials tried to regenerate periodontal ligament (PDL) tissue using PDLSCs; two subcutaneously transplanted and one transplanted into a socket for extraction.

**Dental pulp stem cells**

All included experiments utilizing DPSCs were isolated from human healthy pulp tissues, usually orthodontics, to be used in an animal model. Stem cells from exposed pulp have also been reported to be more likely to differentiate into osteoblastic cells than dentinogenic ones. In this review, 20 articles used DPSCs in mice models, three in rat models, four in dogs, and three in pigs. It was observed that DPSC transplantation was associated with regeneration of pulp-like tissue, successful revascularization, enhanced chondrogenesis, and tissue regeneration with direct vascular supply. However, two studies reported that DPSCs formed an inflamed pulp-like tissue.

**Stem cells from apical papilla**

SCAPs were commonly isolated from immature third molars. Wang et al. reported that SCAPs have greater generation of mineralized tissue than those with DPSCs and higher differentiation of osteo-odontoblast in the supplemental medium kHPO4. Furthermore, SCAPs have been reported to have re-vascularizing properties, heterotopic dental pulp/dentin complex formation, faster proliferation and mineralization, and more efficient migration and telomerase than DPSCs.

**Periodontal ligament stem cells**

PDLSCs demonstrated a significant role in maintenance of MSC characteristics after implantation. In addition, the dentin tissue structure produced by dental follicle cell (DFC) was more complete. In the included experiments, Gao et al. used PDL for regeneration of a fresh bio-root. They developed an effective bio-root of PDL tissue, using a mixture of DPSC-hydroxyapatite wrapped in a layer of PDLSCs. These freshly produced miniature pig roots, both in mineral components and biomechanical characteristics, had comparable characteristics to natural teeth, but only 20% of the samples attained success, whilst titanium implants were 100% effective.

**Bone marrow derived mesenchymal stem cells**

Murakami et al. showed that BMSCs generated a potential pulp, but with less volume. Zhang et al. proposed applying endogenous BM-MSC to a subcutaneous root canal tooth to a regenerative tissue after the systemic homing in the root canal, driven by the use of the stromal cell-derived factor-1 (SDF-1).
| Cell type     | Animal model | Route of administration | Cell type dosage | TERM approach | Co-administrative factors | Coordinating factors | Main results | Reference                                     |
|--------------|--------------|--------------------------|------------------|---------------|---------------------------|---------------------|--------------|----------------------------------------------|
| DPSC         | Mice         | Xenograft subcutaneous   | 5 × 10^6 cells   | AGS           | PLLA/(HA, TCP, CDHA)      | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Wang et al. (2013) |
|              | Rat          | Allogenic transplantation into renal capsule | 5 × 10^6 cells | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Wang et al. (2011) |
|              | Mice         | Xenograft subcutaneous   | 5 × 10^6 cells   | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Zheng et al. (2011) |
|              | Mice         | Xenograft subcutaneous   | 6–12             | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Horibe et al. (2014) |
|              | Mice         | Xenograft subcutaneous   | 4 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Dissantayakul et al. (2014) |
|              | Mice         | Xenograft subcutaneous   | 4 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Wang et al. (2014) |
|              | Mice         | Xenograft subcutaneous   | 4 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Leal et al. (2014) |
|              | Mice         | Xenograft subcutaneous   | 8 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Yang et al. (2012) |
|              | Mice         | Xenograft subcutaneous   | 8 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Wang et al. (2012) |
|              | Mice         | Xenograft subcutaneous   | 12 weeks         | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Chen et al. (2012) |
|              | Mice         | Xenograft subcutaneous   | 16 weeks         | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Wang et al. (2011) |
|              | Mice         | Xenograft subcutaneous   | 8 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Wang et al. (2011) |
|              | Mice         | Xenograft subcutaneous   | 12 weeks         | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Gheller et al. (2011) |
|              | Mice         | Xenograft subcutaneous   | 24 weeks         | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Alongi et al. (2010) |
|              | Mice         | Xenograft subcutaneous   | 24 weeks         | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Gao et al. (2016) |
|              | Pig          | Xenograft subcutaneous   | 3 weeks          | AGS           | PLLA/(TCP, CDHA)         | Collagen            | Implanted DPSC has more tendency to osteogenesis rather than dentinogenesis | Kodonas et al. (2012) |

**Table 1. Summary of included studies.** This table was adapted from a previous systematic review with written permission from the authors and under a Creative Commons Attribution 4.0 International License.
| Cell type | Animal model | Dose & dosage | Co-administrative factors | Route of administration | Co-orthodontic approach | Time point | Main results | Reference |
|-----------|-------------|----------------|--------------------------|-------------------------|-------------------------|------------|--------------|-----------|
| DPSC      | Rabbit      | 5 x 10^6 cells/ml | Autologous intercanal transplantation | Collagen gel | Collagen gel | 12 weeks | Similar tooth structure by different stem cells close to a normal living bone | Hung et al. (2011) |
|           | Rat         | 8 x 10^6 cells/ml | Xenograft intracanal Transplantation | PLLA Nanofibrous spongy microsphere | Alloalloge | 13–26 weeks | Enhanced vascularization | Kung et al. (2016) |
|           | Dog         | 2 x 10^8 cells/ml | Autologous intercanal Transplantation | BMP-2 Collagen gel | Atelo-collagen | 4 weeks | Normal pulp tissue and dentin formation | Nakashima and Iohara (2014) |
|           | Dog         | 1 x 10^7 cells/ml | Autologous intercanal Transplantation | Hypoxic treatment | PLLA Nanofibrous spongy microsphere | 2–17 weeks | Pulp-like tissue regeneration 60% apically, dentin & nerve formation | Iohara et al. (2014) |
|           | Dog         | 1 x 10^6 cells/ml | Autologous intercanal Transplantation | G-CSF | Atelo-collagen | 24 weeks | Generation of pulp-like tissues | Wang et al. (2013) |
|           | Dog         | 1 x 10^6 cells/ml | Autologous intercanal Transplantation | G-CSF | Atelo-collagen | 2–17 weeks | Normal pulp-like tissue and apical secondary dentin formation | Iohara et al. (2018) |
|           | Dog         | 2 x 10^7 cells/ml | Autologous intracanal Transplantation | G-CSF | Clinical grade atelo-collagen | 4 weeks | Enhanced vascularization | Kuang et al. (2016) |
|           | Beagles     | 2 x 10^7 cells/ml | Subcutaneous implantation in mouse of treated human tooth root | Collagen gel | Collagen gel | 24 weeks | Generation of pulp-like tissues | Wang et al. (2013) |
|           | Mice        | 5 x 10^5 cells/ml | Subcutaneous implantation in mouse of human cells | Gel foam | Collagen/PGA | 4–8 weeks | Similar tooth structure by different stem cells close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 2 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen/PG | Collagen/PGA | 24 weeks | Similar tooth structure by different stem cells close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Gelatin | Collagen/PGA | 4–8 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | TCP | TCP | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Gelatin | Collagen/PGA | 4–8 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | TCP | TCP | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Beagles     | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of treated human tooth root | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
|           | Mice        | 1 x 10^6 cells/ml | Subcutaneous implantation in mouse of human cells | Collagen gel | Collagen gel | 24 weeks | Different cell types close to a normal living tooth | Hung et al. (2011) |
| Cell type | Animal model | Route of administration | Dose & dosage | TERM approach | Co-administrative factors | Main results | Reference |
|-----------|--------------|--------------------------|---------------|---------------|---------------------------|--------------|-----------|
| SCAP      | Rat          | Xenograft Transplantation into renal capsule | 1 x 10^6 cells | SCAP pellets/root segment | Polydioxanone Fiber | MTA regulates dentinogenesis of SCAPs | Yan et al. (2014) |
|           | Rat          | Xenograft Subcutaneous Transplantation | 1 x 10^6 cells | SCAP pellets/AGS | VEGF | Blood vessel formation, negligible inflammation | Wang et al. (2013) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 3 x 10^6 cells | BMP-2 | Nuclear Factor IC (NFIC) | More mineralized tissues & higher osteo-odontoblast differentiation in supplemented KH2PO4 medium | Yanlapati et al. (2017) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 3 x 10^6 cells | ntBMP-1 | Wnt3a/Bmp9 | Dentin formation and odontoblast presses inserted to dental tubules | Jin and Cheong (2016) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 1 x 10^7 cells/mL | HA/TCP ceramic powder/fibrin gel | PLLA, NF-MS & PLGA, MS | Mineralization and dentin-like tissue formation | Zhang et al. (2016) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 3 x 10^6 cells | rhPAI-1 | N-Cadherin | Mineralized tissue with embedded cells resembling odontoblasts | Jin and Choung (2016) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 1 x 10^7 cells | HA/TCP | Nuclear Factor I-C (NFIC) | Mineralization & DPC generation equally in SHED Fresh and SHED-Cryo | Casagrande et al. (2012) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 3 x 10^6 cells | Fibrin gel/BB | PLLA | Hard tissue formation (o-SHED > e-SHED) quality of hard tissue (o-SHED = e-SHED) | Jeon et al. (2014) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 2 x 10^6 cells | Macroporous bicrystal calcium phosphate | HA/TCP, PLGA | Mineralization & DPC generation equally in SHED Fresh and SHED-Cryo | Casagrande et al. (2012) |
|           | Mice         | Xenograft Subcutaneous Transplantation | 5 x 10^6 cells | Fibrin gel/BB | PLLA | Mineralization & DPC generation equally in SHED Fresh and SHED-Cryo | Casagrande et al. (2012) |

**Note:**
- SCAP: Stem Cell Adipocyte Precursor
- SHED: Stem Cell Hematopoietic Endoderm
| Cell type | Animal model | Route of administration | Dose & dosage | TERM approach | Co-administrative factors | Main results | Reference |
|-----------|-------------|-------------------------|---------------|---------------|--------------------------|--------------|-----------|
| BMSC      | Mice        | Allograft transplantation into renal capsule | $1 \times 10^7$ cells | G-CSF + TDM + DPEM | Collagen | Local mineralization production of dentin-like tissue | Hashmi et al. (2017) |
| DFSC      | Mice        | Xenograft subcutaneous Transplantation | $1 \times 10^6$ cells | TDM | APES/TPM + DPEM | Polarized cells penetrating into dentin wall | Zhang et al. (2015) |
| PDLSC     | Mouse       | Direct implantation into socket | $1 \times 10^5$ cells | TDM | Human, TDM and CDM | Participation of systemic BMSC in introral dentin-pulp-like tissue | Murakami et al. (2015) |
| ADSC      | Rat         | Allograft transplantation into the extracted socket | $5 \times 10^6$ cells | TDM | BMP-2 | Potential pulregeneration in MADSC & MEBMSC but in less volume | Cheron et al. (2015) |
| RPSC      | Rat         | Allograft transplantation into renal capsules | $1 \times 10^6$ cells | TDM | AGS | Potential pulregeneration in MADSC & MEBMSC but in less volume | Cheron et al. (2015) |
| PDLSC     | Rabbit      | Allograft transplantation into the extracted socket | $5 \times 10^6$ cells | TDM | BMP-2 | Potential pulregeneration in MADSC & MEBMSC but in less volume | Cheron et al. (2015) |
| ADSC      | Rat         | Allograft transplantation into the extracted socket | $10^6$ cells | TDM | BMP-2 | Potential pulregeneration in MADSC & MEBMSC but in less volume | Cheron et al. (2015) |
| Cell type            | Animal model | Dose & dosage | Route of administration                              | Co-administrative factors | TERM approach | Time point | Main results                                                                 | Reference         |
|----------------------|--------------|---------------|-------------------------------------------------------|---------------------------|---------------|------------|--------------------------------------------------------------------------------|-------------------|
| Mesenchymal          | Mice         | $2 \times 10^5$ cells | Rat to mice Transplantation intorenal capsule         | hBMP4 hBMP7                | PLGA          | 8 weeks    | Enamel and dentin-like tissues generation in two integrated layers with amelogenin expression and amelo blastin | Jiang et al. (2014) |
| UCMSC                | Mice         | $5 \times 10^4$ cells/well | Xenograft subcutaneous Transplantat                   | hTDM                      | TDM           | 8 Weeks    | Formation of layers and calcifications                                          | Chen et al. (2015) |
| Human DP Progenitors | Mice         | $10^4$ cells/50 μl | Xenograft subcutaneous Implantation                   | Stem cell factor (SCF)    | Collagen sponge | 4 weeks    | Induction of cell homing, angiogenesis, and tissue remodeling                   | Pan et al. (2013)  |
| Dermal multipotent cells | Mice      | $2.0 \times 10^6$ cells | Xenograft subcutaneous transplantation                | Embryonic and neonatal TGC-CM | Fibrin gel       | 4 weeks    | Bone like structure formation from embryonic TGC-CM                           | Huo et al. (2010)  |
| DBCs                 | Porcine      | $1 \times 10^7$ cells | Autotransplantation into swine’s original alveolar socket | GCHT                      | Gelatin-chondroitin-hyaluronan-tricopolymer | 36 weeks   | Successful rate of tooth regeneration from DBCs/GCHT scaffolds’ was about 33.3% | Kuo et al. (2007)  |
| NA                   | Beagles      | NA            | Cell homing                                          | SDF-1α                     | Silk/Fibrin    | 12 weeks   | Pulp tissue generation and mineralization along dental wall                    | Yang et al. (2015) |

BC, blood clot; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BMSC, bone marrow mesenchymal stem cell; CC, costal chondrocyte; CDHA, calcium carbonate hydroxyapatite; CNCC, cranial neural crest cell; CXCL14, chemokine (CXC motif) ligand-14; DFSC, dental follicle stem cell; DPSC, dental pulp stem cell; FGF, fibroblast growth factor; GCSF, granulocyte colony-stimulating factor; GF, growth factors; HA, hydroxyapatite; IPS, induced pluripotent stem cell; MCP1, monocyte chemoattractant protein-1; MSC, mesenchymal stem cell; MTA, mineral trioxide aggregate; NA, not exogenously added; ND, not determined; NGF, nerve growth factor; PCL, polycaprolactone; PGA, polyglycolic acid; PGDF, platelet-derived growth factor; PLGA, poly-L-lactic acid; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; REP, regenerative endodontic procedure; SCAP, stem cell of the apical papilla; SHED, stem cell from human exfoliated deciduous teeth; TCP, tricalcium phosphate; TDM, treated dentin matrix; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; DBCs, dental bud cells.
Table 2. Variations of extracted data from reviewed articles.

| Variables          | Number of studies (%) |
|--------------------|-----------------------|
| Cell type          |                       |
| DPSCs              | 31 (46)               |
| SCAP               | 8 (12)                |
| DFSC               | 6 (9)                 |
| BMSC               | 4 (6)                 |
| SHED               | 4 (6)                 |
| PDLSC              | 3 (4.4)               |
| ADSC               | 1 (1.5)               |
| Other              | 7 (10.4)              |
| Scaffold           |                       |
| Collagen           | 15 (22.3)             |
| TDM                | 9 (13.4)              |
| HA/TCP             | 10 (15)               |
| PLLA               | 6 (9)                 |
| PLGA               | 4 (6)                 |
| Atelocollagen      | 4 (6)                 |
| Fibrin gel         | 8 (12)                |
| CBB                | 3 (4.4)               |
| Silk fibroin       | 1 (1.5)               |
| Other              | 3 (4.4)               |
| Growth factors     |                       |
| TDM                | 9 (13.4)              |
| BMP                | 5 (7.4)               |
| G-CSF              | 5 (7.4)               |
| SDF-1              | 3 (4.4)               |
| VEGF               | 3 (4.4)               |
| b-FGF              | 3 (4.4)               |
| Other              | 35 (52.2)             |
| Transplantation site |                   |
| Subcutaneous       | 40 (59.7)             |
| Inter canal        | 4 (6)                 |
| Renal capsule      | 8 (12)                |
| Into socket        | 3 (4.4)               |
| Other              | 8 (12)                |
| Animals            |                       |
| Mice               | 44 (65.6)             |
| Rat                | 7 (10.4)              |
| Pig                | 4 (6)                 |
| Dog                | 7 (10.4)              |
| Rabbit             | 2 (2.9)               |
| Beagles            | 2 (2.9)               |

*The number of included studies is 57 studies; however, the number of trials is 67 trials. Therefore, each study may include one or more types of cells. BC, blood clot; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BMSC, bone marrow mesenchyme stem cell; CC, costal chondrocytes; CDHA, calcium carbonate hydroxyapatite; CNCC, cranial neural crest cell; CXCL14, chemokine (CXC motif) ligand-14; DFSC, dental follicle stem cell; DPSC, dental pulp stem cell; FGF, fibroblast growth factor; GCSF, granulocyte colony-stimulating factor; GF, growth factors; HA, hydroxyapatite; IPS, induced pluripotent stem cell; MCP1, monocyte chemotactic protein-1; MSC, mesenchymal stem cell; MTA, mineral trioxide aggregate; NA, not exogenously added; ND, not determined; NGF, nerve growth factor; PCL, polycaprolactone; PGA, polyglycolic acid; PGDF, platelet-derived growth factor; PLGA, polyactide-co-glycolic acid; PLLA, poly-L-lactic acid; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; REP, regenerative endodontic procedure; SCAP, stem cell of the apical papilla; SHED, stem cell from human exfoliated deciduous teeth; TCP, tricalcium phosphate; TDM, treated dentin matrix; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

Use of dentine-matrix-scaffolding cells was associated to the differentiation of the stem cells in a dentinal tubule in polarized odontoblast-like cells\(^62\).

**Stem cells from human exfoliated deciduous teeth**

SHEDs, which rare derived from extracted deciduous teeth, were used in mice models in four studies\(43,58-60\). It was observed that the capability of mineralization of SHEDs was higher than DPSCs\(^43\). Casagrande et al.\(^{60}\) reported that SHEDs express markers of odontoblastic differentiation (DSPP, DMP-I, MEPE).

**Discussion**

This is the largest and most updated systematic review aiming to investigate the role of DSCs in tooth repair. We found that multiple DSCs have a potent role in tissue regeneration and vascularization of dental pulp-like tissues\(44,56,59,61,66,70,72\). Most of the included research assessed the 4–8 week dentine-pulp regeneration following transplant\(67,69,70\). These studies used the ectopic models of dentine pulp-complex. A few studies used long-term evaluation of up to 36 weeks after surgery\(^1\). However, there are some studies that had multiple time points for evaluation.

Like other tissues, three primary components are required to regenerate a necrotic pulp: 1) vital root canal cells, which can distinguish into normal pulp cells, 2) morphogenic and growth factors to activate and encourage cell distinction, and 3) a matrix that ensures an environment that maintains their vitality and growth and supports cells in a mechanical way\(58,69,71\).

Growth factors, drugs, bioactive products, glycosaminoglycans and other small molecules and motifs of peptide are considered promotive healing factors that can be used for stem cells and matrix to improve the effectiveness of stem cell therapy for dentine-pulp regeneration and biodegradation. Growth factors have a short half-life; therefore, degradable materials are required to control their release\(47,48,73\).

Recent studies for dentine pulp regeneration have been done in various types of stem cells from various sources in body. DPSCs are the preferred cells in the majority of these studies and have demonstrated their capacity to regenerate the complex dentine\(1,22,23,46,65\). Although the great tendency for dentine-pulp complex regeneration, SCAP and SHED were rarely administered\(^{14,71}\). DPSCs and SHEDs were evaluated with adequate or partly successful histological outcomes in various REP research. DPSC, collagen or poly(lactide/glycolide and scarce factors with or without growth factors are optimized when compared to REPs with growth factors but without amplified stem cells\(^{10}\). Several dentin therapies demonstrate further excellent outcomes, which should be followed by platelet-rich plasma/platelet-rich fibrin (PRP/PRF) or collagen gels in REPs and improved biomimicry to maintain various levels of the variables that release oral stem cell niche formation. Recently, cell survival of stem cells is much easier than in the past due to the appropriate interaction with dentine-released factors\(^2,22\). Thus, screening for more appropriate stem cells, dentine releasing treatments, scaffolds with good biomimicry and good histological markers is an exciting activity for future REP improvements.
Besides dental sources, non-dental cells, such as the MSCs derived from bone marrow and adipose stem cells, are able to regenerate the pulp tissue.

Generally, our study showed that adult stem cells appear to be able to regenerate dentine-pulp complexes; therefore, the criteria of selection should be considered the most cost-effective and cheapest, particularly when the main obstacle is the expense. Moreover, our findings demonstrated that the human body is a wealthy source of stem cells; therefore, the third molars or any orthodontic tooth originated from a human body are excellent sources of stem cells. As regards cells circulating, these cells migrate to sites and engage in a recovery process in the presence of chemotactic gradients, as their capacity for root canal migration was shown.

This study showed two limitations; 1) we could not conduct a meta-analysis due to insufficient data; and 2) we failed to find a suitable tool to assess the quality of included studies and risk of bias.

In conclusion, the current evidence suggests that the DPSCs, SHEDs, and SCAPs are capable of providing a sufficient pulp regeneration and vascularization. Nevertheless, the efficacy of stem cell transplantation in therapy locations and their cost may be obstacles to their clinical use. Scaffolds and biomaterials provide a useful strategy for stronger incorporation of stem cells and development factors together with monitored regeneration rates. Hence, we suggest future studies to concentrate on offering definite guidance on appropriate and preferable biomaterial characteristics for use in regenerative endodontics.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for ‘Dental stem cells in tooth repair: A systematic review’, https://doi.org/10.6084/m9.figshare.10315835.v1.

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Open Peer Review

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In this review, the authors summarized recent studies of dental pulp regeneration using stem cells. In general, it is a timely and detailed review of stem cells used in dental regeneration. But this manuscript needs to be carefully modified.

Comments:
1. In the abstract and Table 2, the authors described “TDM (treated dentin matrix)” as a growth factor. In fact, TDM is a matrix containing growth factors. “Growth factors derived from TDM” is more suitable.

2. The language of this manuscript should be checked and polished by a native English speaker.

3. According to the methods, the authors searched the databases from January 2000 to June 2019: Since numbers of studies of dental pulp regeneration have published after June 2019, it is recommended for the authors to update their data to June 2020.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dental regeneration

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 21 January 2020

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The manuscript “Dental stem cells in tooth repair: A systematic review” is a review by Tadros et al. on a very timely topic, tooth regeneration. However, this paper does not read like a review but rather as a catalogue of papers. This review requires conceptual work towards synthesizing the great findings in the field. For example, many notable, recent papers are excluded from this review. In addition, the following comments need to be addressed.

- Provide citations for every statement (e.g. “Loss of tooth pulp stops the development of permanent root teeth that can weaken the periodontal connection and lead to teeth loss” Page 3, Paragraph 2.)

- Spelling and grammar review. Multiple incidences of unclear sentences (e.g. “Although the great tendency for dentine-pulp complex regeneration, SCAP and SHED were rarely administered.” Page 10, Paragraph 5) or incorrect word used (“SHEDs, which rare derived from extracted deciduous teeth” Page 10, Paragraph 1).

- Develop appropriate tool to assess the quality of included studies and risk of bias such as that described in Cochrane Handbook for Systematic Reviews of Interventions.
  - Why were studies excluded/removed?
  - What databases/sources were used?
  - What search terms were used?
  - Studies included:
    - Reviews are not listed though there are reviews included.
    - Humans are not listed in populations studied though human studies are cited
(e.g. “All included experiments utilizing DPSCs were isolated from human healthy pulp tissues...” Page 4, Paragraph 3).

- Why there was insufficient data for meta-analysis.
- Meaning of “usually orthodontics” Page 4, Paragraph 3. Does this mean teeth were extracted due to orthodontic treatment plans?
- “Fresh bio-root” and “success” when discussing PDLSCs and “potential pulp” on Page 4, Paragraph 4 and 5.
- TERM approach.
- “Scarce factors” and “excellent outcomes” discussed on Page 10, Paragraph 5.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

No

**Are sufficient details of the methods and analysis provided to allow replication by others?**

No

**Is the statistical analysis and its interpretation appropriate?**

Not applicable

**Are the conclusions drawn adequately supported by the results presented in the review?**

No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** stem cells and regeneration

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.
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