



Review

Chondrogenic Potential of Dental-Derived Mesenchymal Stromal Cells

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Featured Application: As an answer to the ongoing search for the ideal source of Mesenchymal Stromal Cells (MSCs) for cartilage tissue engineering, dental issues offers a variety of MSC source in its vicinity. If its chondrogenic potential is validated in future clinical trials, dental tissues would prove to be worth banking for the array of MSC sources it offers.



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Abstract: The field of tissue engineering has revolutionized the world in organ and tissue regeneration. With the robust research among regenerative medicine experts and researchers, the plausibility of regenerating cartilage has come into the limelight. For cartilage tissue engineering, orthopedic surgeons and orthobiologists use the mesenchymal stromal cells (MSCs) of various origins along with the cytokines, growth factors, and scaffolds. The least utilized MSCs are of dental origin, which are the richest sources of stromal and progenitor cells. There is a paradigm shift towards the utilization of dental source MSCs in chondrogenesis and cartilage regeneration. Dental-derived MSCs possess similar phenotypes and genotypes like other sources of MSCs along with specific markers such as dentin matrix acidic phosphoprotein (DMP) -1, dentin sialophosphoprotein (DSPP), alkaline phosphatase (ALP), osteopontin (OPN), bone sialoprotein (BSP), and STRO-1. Concerning chondrogenicity, there is literature with marginal use of dental-derived MSCs. Various studies provide evidence for in-vitro and in-vivo chondrogenesis by dental-derived MSCs. With such evidence, clinical trials must be taken up to support or refute the evidence for regenerating cartilage tissues by dental-derived MSCs. This article highlights the significance of dental-derived MSCs for cartilage tissue regeneration.

Keywords: dental pulp; mesenchymal stromal cell; chondrogenicity



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1. Impact Statement

Dental tissues are the richest sources of mesenchymal stromal cells, which are not much used in clinical practice. Researchers and regenerative medicine clinicians are more interested in exploring the regenerative potential of dental-derived MSCs, which can be translated from bench to bedside clinical applications. The evidence stated that dental-derived MSCs can be used for cartilage regeneration. To explore the chondrogenicity of dental-derived MSCs, clinical trials have to be taken up to support or refute the evidence for cartilage regeneration.

2. Introduction

Cartilage is an avascular and aneural structure with poorly cellularized connective tissue [1,2]. Cartilage tissue facilitates mechanical load transmission with a low frictional coefficient resulting in cartilage injury that has an inherent limited healing potential [3]. The recent idea of “Orthobiologics” led to the exploration of stem cells and regenerative medicine in treating musculoskeletal disorders [4]. Orthobiologics provide administration of osteoinductive and osteoconductive micromolecules to enhance regeneration of degenerated tissues, tendons, bones, and cartilages [4].

Tissue Engineering (TE) is defined as in-vitro or in-vivo regeneration of tissues for repairing and replacing the diseased tissue or organ to enhance and restore the tissue function and maintain tissue homeostasis and improve the biomechanical strength of the tissues [5–7]. Cartilage tissue engineering provides a new strategy by transplanting chondrogenic cells along with biocompatible 3D scaffolds and micromolecules to produce engineered cartilage tissue [6,8]. Chondrogenic cells are derived from mesenchymal stromal cells from various sources, namely, bone marrow [9], adipose tissue [10], placenta [11], amniotic fluid [12], Wharton jelly [13], umbilical cord [14], synovium [15], hair follicles [16], dental pulp [17], and gingiva [18]. The tissue engineering triad comprises mesenchymal stromal cells, scaffolds, and biomolecules such as growth factors and cytokines [8,19].

Mesenchymal stromal cells (MSCs) form an integral part of regenerative medicine for cartilage regeneration. MSCs are multipotent stem cells with clonogenicity, plasticity, self-renewal, and differentiation [20,21]. MSCs differentiate into trilineage namely osteogenesis, chondrogenesis, and adipogenesis [22–24]. Chondrogenesis is mediated by various mediators such as TGF- β 1 and - β 3; BMP-2, -4, and -7; IGF-1; and GDF-5 [25,26]. Dental structures provide a variety of stem cells with ease of isolation, non-invasiveness, and availability [17,27,28]. Stem cells of dental origin have similar properties of multipotency, diverse differentiative potential, anti-inflammation, immunomodulation, immune privilege like BM-MSCs, AD-MSCs, and Sy-MSCs [29,30]. This article throws light on MSCs of dental origin in chondrogenesis and cartilage regeneration in osteoarthritic knees.

3. MSCs of Dental Origin

Stem cells of dental origin form a good therapeutic paradigm in regenerating tissues, bones, and cartilage. MSCs of dental origin include (a) dental pulp MSCs (DP-MSCs) [31,32], (b) stem cells from human exfoliated deciduous teeth (SHEDs) [33,34], (c) periodontal ligament stem cells (PDLSCs) [35,36], (d) dental follicle precursor cells (DFPCs) [37,38], (e) stem cells from apical papilla (SCAPs) [39,40], and (f) gingival derived MSCs (G-MSCs) [41,42]. Among all these sources of dental stem cells, researchers pay attention to DP-MSCs and SHEDs because of ease in their accessibility. The various sources of MSCs of dental origin are shown in Figure 1.

3.1. Dental Pulp MSCs (DP-MSCs)

Embryologically, dental pulp arises from ectomesenchyme where the periphery of the neural tube gives rise to ectodermal cells and migrates to the oromaxillary region, and differentiates into mesenchymal phenotype. The dental pulp remains an unmineralized connective tissue that comprises a heterogeneous population including stromal cells, progenitors, odontoblasts, ameloblasts, fibroblasts, granulocytes, macrophages, vascular fragments, capillaries, and extracellular matrices. Dental pulp tissue is the richest source of MSCs, which are extracted from the teeth recovered during routine dental procedures [32]. DP-MSCs are isolated from impacted third molars and supernumerary teeth, which possess extreme clonogenicity, plasticity, regenerative and reparative potential [43,44]. These cells reside within the dental crown called “niche” or “pulp chamber” [45]. The usage of DP-MSCs was documented with diabetes mellitus [46], neurological disorders [47], maxillofacial and dental disorders [48], disorders of bone and cartilage [49], hepatic disorders [50], and immunological diseases [51]. The extraction of MSCs from dental structures remains non-invasive and can be cryopreserved for future usage.

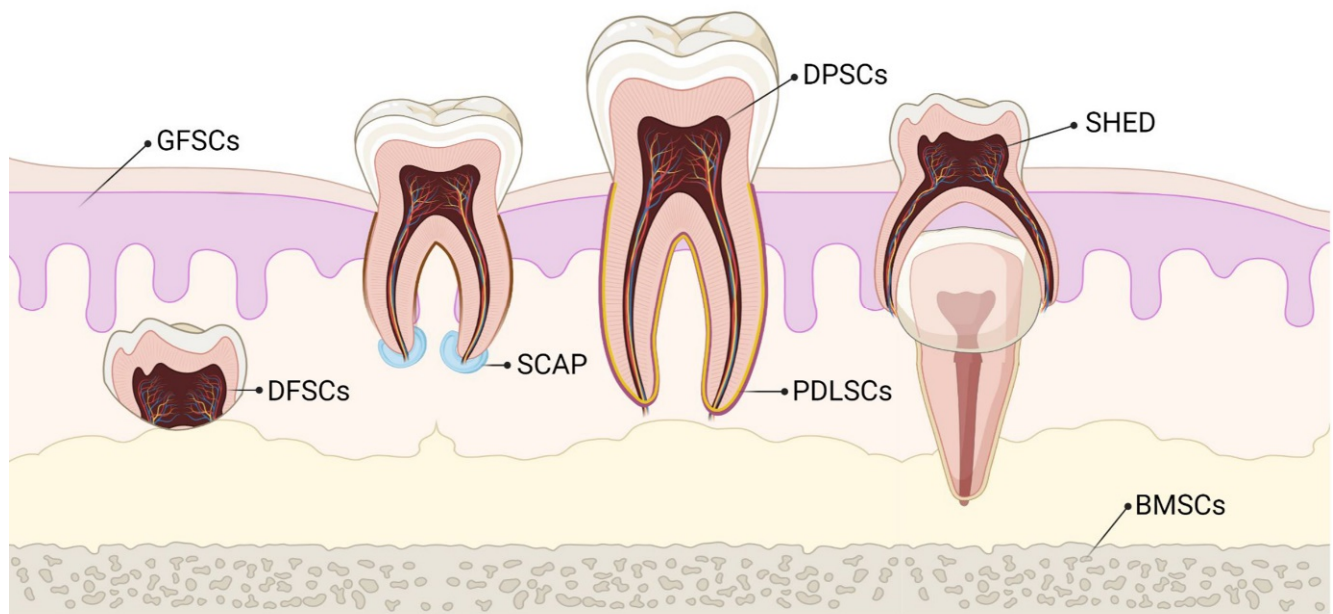


Figure 1. Various sources of stem cells of dental origin. BMSCs–Bone Marrow Stem Cells; DFSCs–Dental Follicle Stem Cells; DPSCs–Dental Pulp Stem Cells; GFSCs–Gingival Fibroblastic Stem Cells; PDLSCs–Periodontal Ligament Stem Cells; SCAP–Stem Cells of Apical Papilla; SHED–Stem cells of Human Exfoliated Deciduous teeth.

During dentinogenesis, the interplay between dental pulp epithelial cells leads to the differentiation of odontoblasts and ameloblasts, which deposit dentin and enamel, respectively. The inner lining of dental pulp contains progenitor cells with high regenerative potential throughout the lifetime [52]. DP-MSCs possess a similar regenerative potential to BM-MSCs, but DP-MSCs act as a non-invasive source for extraction of MSCs for therapeutic usage in various diseases [51,53].

Upon addition of appropriate growth factors, micromolecules, transcriptional factors, and ECM proteins, DP-MSCs differentiate into multilineages, namely, adipogenesis, chondrogenesis, osteogenesis, neurogenesis, and dentinogenesis both in in-vitro and in-vivo studies [54,55]. During any insult to dental structures, due to the higher proliferative capacity, the quiescent DP-MSCs activate and immediately differentiate into ameloblasts, odontoblasts, osteoblasts, adipocytes, and chondrocytes to produce dentin, bone, fat, and cartilage for their repair process, respectively [27,56]. Yu et al. demonstrated the reduced odontoblastogenesis after the ninth passage and differentiation of osteoblast precursors [57]. Since DP-MSCs are derived from the neural crest, they possess neural crest stem cell markers and hence they differentiate into neuron-like cells [58–60]. Superior chondrogenesis was exhibited by DP-MSCs both in-vitro and in-vivo when compared with BM-MSCs [61–64].

3.2. Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs)

SHEDs are stromal cells extracted from exfoliated deciduous teeth, which behave in the line of embryonic stem cells [65]. They possess MSC markers, epidermal stem cell markers, and tumor recognition markers, but do not exhibit hematopoietic stem cell markers [66]. SHEDs demonstrate higher proliferation and differentiation ability and form cell cluster formation like a sphere when compared with DP-MSCs [67,68]. They enhance osteogenic differentiation due to the presence of higher levels of osteocalcin, and alkaline phosphatase. SHEDs when mixed with platelet-rich plasma, the osteogenic response accelerated in mandibular defects in canines [69] SHEDs play a major role in treating diabetes mellitus [70,71] and neurological disorders such as spinal cord injury [72], focal cerebral ischemia [73,74], and Alzheimer's disease [75,76]. Muhammad et al. observed the upregulation of MMP-13, NF- κ B, aggrecan, ECM proteins, and COL-2 in the regenerated chondrocytes with SHEDs, which underscored the basis for OA knee management [77].

3.3. Periodontal Ligament Stem Cells (PDLSCs)

PDLSCs are situated in the perivascular wall of periodontal ligaments and mimic pericytes with diverse differentiation and regeneration potential and their ability to form capillary-like structures in-vitro [78,79]. On their cell surface, they show pericyte-associated markers CD-146, and -140B and neural/glial antigen-2 [79,80]. PDLSCs are isolated from the mid-third portion of the root surface after permanent tooth extraction and alveolar socket [78]. Wang et al. reported that alveolar socket-derived PDLSCs possess higher proliferative and differentiative potential than root-derived PDLSCs [81]. Silverio et al. emphasized that deciduous teeth-derived PDLSCs (d-PDLSCs) possess greater proliferation, stronger adipogenic, and osteogenic potential than permanent teeth-derived PDLSCs (p-PDLSCs) [82]. PDLSCs possess strong immunomodulatory, anti-fibrotic, and anti-inflammatory capacities like BM-MSCs and AD-MSCs [83,84]. PDLSCs enhance chondrogenesis by the addition of TGF- β 3 and BMP-6. In tissue analysis, there was increased expression of SOX-9, TGF- β 3, BMP-6, aggrecan, COL-2, and 10 and Runx2 in the chondrogenic cells [30].

3.4. Dental Follicle Precursor Cells (DFPCs)

The dental follicle (DF) is a loose connective tissue derived from ectomesenchyme that surrounds the tooth germ [85]. Compared to other stem cells of dental origin, DFPCs exhibit robust immunomodulation, proliferative and diverse differentiative potential [37,86]. Evidence proved that DFPCs differentiate into the alveolar bone, PDL, cementum, adipocyte, osteoblast, cementoblast/chondrocyte, neuron-like cell cardiomyocyte, and dentin-like tissues [45,85]. Researchers have extensively utilized DFPCs for regenerating bone defects, cartilage engineering, tooth root, and periodontal tissue regeneration, and neural tissue regeneration. DFPCs express NOTCH-1 transmembrane protein, which decides the fate of the cell to be differentiated and HLA-ABC, which is acquired during culture [87]. When co-cultured with lymphocytes, DFPCs exhibit decreased INF- γ and IL-4 and increased IL-6, and -10 and TGF- β . Transplanted DFPCs regenerate bone in the calvarial defect when loaded with polycaprolactone (PCL) scaffold along with hyaluronate and β -tricalcium phosphate [88]. Periodontal osteogenesis of DFPCs is enhanced with nanosilicates and fluoride additives [89].

3.5. Stem Cells from Apical Papilla (SCAPs)

SCAPs are a novel group of MSCs that reside inside the apical papilla of immature permanent teeth [90]. SCAPs possess superior osteogenic differentiation potential [90,91] and inferior adipogenic differentiation potential than BM-MSCs [91,92]. Inherently, SCAPs contain enormous levels of dentin sialophosphoprotein, bone sialoprotein, alkaline phosphatase, bone γ -carboxyglutamate protein, BMP-2, -7 and -9, and Runt-related transcription factor 2 renders them more osteogenic potential [93]. SCAPs exhibit an innate property for neoangiogenesis due to the presence of VEGF, bFGF, MMPs, IGF-BP3, and thrombospondin-1 [94,95]. When induced with platelet lysate or growth factors, SCAPs show a greater proliferation rate [95,96]. While compared with DP-MSCs, SCAPs exhibit higher levels of survivin, longer telomere length with higher telomerase activity, increased cellular turnover and proliferation rate [97,98]. They secrete significantly higher amounts of chemokines, neurotrophins, transcription proteins, and growth factors than BM-MSCs [99]. With knock-down of LINC01013, SCAPs enhance chondrogenic differentiation and proliferation by the increased expressions of DLX-5, HOXC8, COL-2 and -5, and SOX-9 in a pellet culture system [47,100].

3.6. Gingival-Derived MSCs (G-MSCs)

Gingiva becomes a more readily available and accessible source of stem or progenitor cells in the oral cavity. G-MSCs are extracted from gingival lamina propria and free or inflamed or hyperplastic gingiva [101,102]. When transplanted to the site of action, G-MSCs form connective tissue-like structures along with extracellular matrices than other sources

of dental stem cells [57,58]. This property draws great attention among regenerative specialists to explore more on G-MSCs. G-MSCs are easy to isolate and extract from naïve tissues, uniformly homogeneous, possess stable phenotype, cellular turnover, and proliferation rate, maintain telomerase activity in long-term cultures and higher grade passages [103,104]. G-MSCs promotes macrophage polarization to the M2 phenotype and provides an anti-inflammatory environment in the wound bed and promotes vasculogenesis and enhances wound repair [105]. Injection of biodegradable TGF- β 3-loaded hydrogel microspheres along with clinical-grade G-MSCs enhance tendon regeneration in an immunocompromised mouse [106]. Wang et al. demonstrated bone regeneration in mandibular and calvarial defects in rats within two months of transplantation of G-MSCs [107].

4. Characterization of Dental-Derived MSCs (D-MSCs)

DP-MSCs and SHEDs possess similar immunophenotype like BM-MSCs, AD-MSCs, and Sy-MSCs [108–110]. DP-MSCs and SHEDs possess cell markers of MSCs (CD-13 [alanyl aminopeptidase], -44, -73 [ecto-5'-nucleotidase], -90, -105 [endoglin], -146, and -166, STRO-1) [111], osteogenic markers (BMP-2, OCN, OPN, osteonectin, and COL-1) [112], adipogenic markers (LPL and PPAR- γ) [113], chondrogenic markers (SOX-9 and COL-2) [110,112], myogenic markers (myosin, myogenin, and SMA- α) [114], neurogenic markers (nestin, GFAP, MAP-2, and β 3 tubulin) [115–117], and pluripotency markers (OCT-4, SOX-2, Nanog, and IGF-1R) [118,119]. They demonstrate negative staining for hematopoietic markers (CD-14, -19, -34, -45, and HLA-DR) [109,120].

The specific markers for D-MSCs are markers of odontoblast differentiation [dental matrix protein-1 (DMP-1) and dentine sialophosphoprotein (DSPP)] [121], markers of extracellular matrix [alkaline phosphatase (ALP)] [122], markers of osteogenic differentiation [osteopontin (OPN)] [123], markers of mineralized tissue differentiation [bone sialoprotein (BSP)] [124], and markers of differentiating potential of D-MSCs [STRO-1] [125].

Biodentine, a bioactive dentine substitute, is capable of inducing DP-MSCs differentiation of odontoblasts. Luo et al. demonstrated odontoblast differentiation of DP-MSCs by increased expression of ALP, OCN, DSPP, DMP1, and BSP [126]. Optimal mechanical compression increased the expression of DSPP, BMP-7, and Wnt10a genes for odontoblast differentiation by DP-MSCs [127]. BBX gene expression induces the differentiation of odontoblasts by DP-MSCs [128]. DNA methylation and PTEN expression were increased in DP-MSCs, which are responsible for lineage differentiation and reduced oncogenesis when compared with BM-MSCs [129]. The differential characteristics of individual MSCs of dental origin are given in Table 1.

Table 1. Characteristics of dental-derived MSCs. DFSCs–Dental Follicle Stem Cells; DPSCs–Dental Pulp Stem Cells; GFSCs–Gingival Fibroblastic Stem Cells; PDLSCs–Periodontal Ligament Stem Cells; SCAP–Stem Cells of Apical Papilla; SHED–Stem cells of Human Exfoliated Deciduous teeth (++ low; +++ medium; ++++ high; ↑increased; ↓decreased).

| Type of Dental-Derived MSCs | CD Markers | | Proliferative Potential | Differentiative Potential | Immunomodulatory Capacity | Clinical Application |
|-----------------------------|--|--|-------------------------|--|--|--|
| | Positive | Negative | | | | |
| DP-MSCs | CD-9, -10, -13, -29, -44, -59, -73, -90, -105, -146, -106, -146, -166, -271, STRO-1, TRA1-60, NANOG, SOX-2, Oct-4, and TRA-1-80-1 | CD-14, -19, -24, -117, -34, -45, -31, and -133 | +++ | Adipocyte, dentin-pulp, bone muscle/odontoblast, myoblast adipocyte, osteoblast, neuron-like cell, cardiomyocyte, and hepatocyte-like cell | ↑ HGF, TGFβ, PGE-2, IL-6, IDO, and IL-10 ↓ IL-4 and IFN-γ; ↑ number of Tregs; ↓ proliferation of T cells and PBMCs; Inducing activated T cells apoptosis | Bone defects, dentin pulp repair, neural tissue regeneration, diabetes mellitus, immunological disorders, and chondrogenesis |
| SHED | CD-29, -73, -90, -105, -146, -166, STRO-1, NANOG, and nestin | CD-14, -34, and -45 | ++ | Bone dentin-pulp, microvessels/chondrocyte, myocytes, adipocytes, osteoblasts, and neuron-like cell | Inhibited Th17 cell differentiation; ↑ number of Tregs; Corrected CD4+ T cell immune imbalance in allergic diseases; ↑ IL-10 and ↓ IL-4 and IFN-γ | Craniofacial bone defects, dentin-pulp repair, neural regeneration, tooth root regeneration, diabetes mellitus, spinal cord injury, focal cerebral ischemia, and Alzheimer's disease |
| PDLSCs | CD-9, -10, -13, -29, -44, -59, -73, -90, -105, -106, -146, -166, -271, and STRO-1 | CD-11b, -14, -19, -34, -45, -79α, and HLA-DR | ++ | Cementum, PDL/chondrocyte, osteoblast, cementoblast, adipocyte, and neuron-like cell | ↑ expression of TLR-2 and -4; ↑ release IDO, HGF, and TGFβ; ↓ proliferation of PBMCs and reduced induction of Tregs | Tooth root and periodontal tissue regeneration |
| DFSCs | CD-9, -10, -13, -29, -44, -53, -56, -59, -73, -90, -105, -106, -146, -166, -271, STRO-1, NOTCH-1, HLA-ABC, NANOG, SOX-2, OCT-4, nestin, and β3-tubulin | CD-31, -34, -45, and -133 | ++++ | Alveolar bone, PDL, cementum, adipocyte, osteoblast, cemento-blast/chondrocyte, neuron-like cell cardiomyocyte, and dentin-like tissue | ↑ expression of TLR-2, -3, and -4; ↑ IL-10, IL-6, TGFβ, and IDO-1; ↓ IFN-γ, IL-4, and IL-8; ↓ proliferation of PBMCs; ↓ number of CD4+ T cells and ↑ Tregs | Bone defects, cartilage engineering, tooth root, and periodontal tissue regeneration, and neural tissue regeneration |

Table 1. Cont.

| Type of Dental-Derived MSCs | CD Markers | | Proliferative Potential | Differentiative Potential | Immunomodulatory Capacity | Clinical Application |
|-----------------------------|---|---------------------------|-------------------------|--|---|---|
| | Positive | Negative | | | | |
| SCAP | CD-13, -29, -49, -51, -56, -61, -73, -146, -90, -44, -24, -106, -146, -166, STRO-1, NANOG, and nestin | CD-14, -18, -34, and -45 | ++ | Dentin-pulp/osteoblast, adipocyte, odontoblasts, hepatocytes, and neuron-like cell | Inhibited proliferation of T cells; Overexpressed Nfic to suppress LPS-initiated innate immune responses | Bone regeneration, tooth root regeneration, dentin-pulp repair, neural regeneration |
| GFSCs | CD-29, -44, -73, -90, -105, -106, -166, STRO-1, NANOG, and nestin | CD-14, -117, -34, and -45 | ++ | Cartilage, bone, muscle/adipocyte, chondrocyte, osteocyte, and neuron-like cell | ↑ expression of TLR-1, -4, -5, -7, and -10; Inhibited proliferation of T cells and Th17; ↑ CD4+ CD25+ FoxP3+ Tregs; releasing IL-6, IDO, IL-10, COX-2, and iNOS | Calvarial defects, neural regeneration, and periodontal regeneration |

5. Harvesting and Delivery Methods of D-MSCs

Various regenerative medicine experts followed different methods to extract and harvest stromal cells from dental pulp.

Raouf et al. used three different methods to isolate DP-MSCs, namely, (a) digestion of dental pulp tissue with collagenase and placement of isolated trypsinized cells in petri dishes, (b) explantation of undigested dental pulp pieces to culture plates, and (c) explantation of trypsinized dental pulp tissues to petri dishes for outgrowth [130]. These tissues are plated to MEM medium supplemented with 20% fetal bovine serum at 37 °C with a 5% CO₂ incubator. A total of 60% cellular confluency was achieved within days of culture and checked for pluripotency markers by RT/PCR analysis [130].

Naz et al. expanded DP-MSCs and SHEDs via the explant culture method after extirpation of dental pulp tissues from deciduous teeth [131]. As a result of culture expansion, MSCs exhibit fibroblast-like cells with long cytoplasmic processes. DP-MSCs and SHEDs characterization was done and cryopreserved for future use as shown in Figure 2.

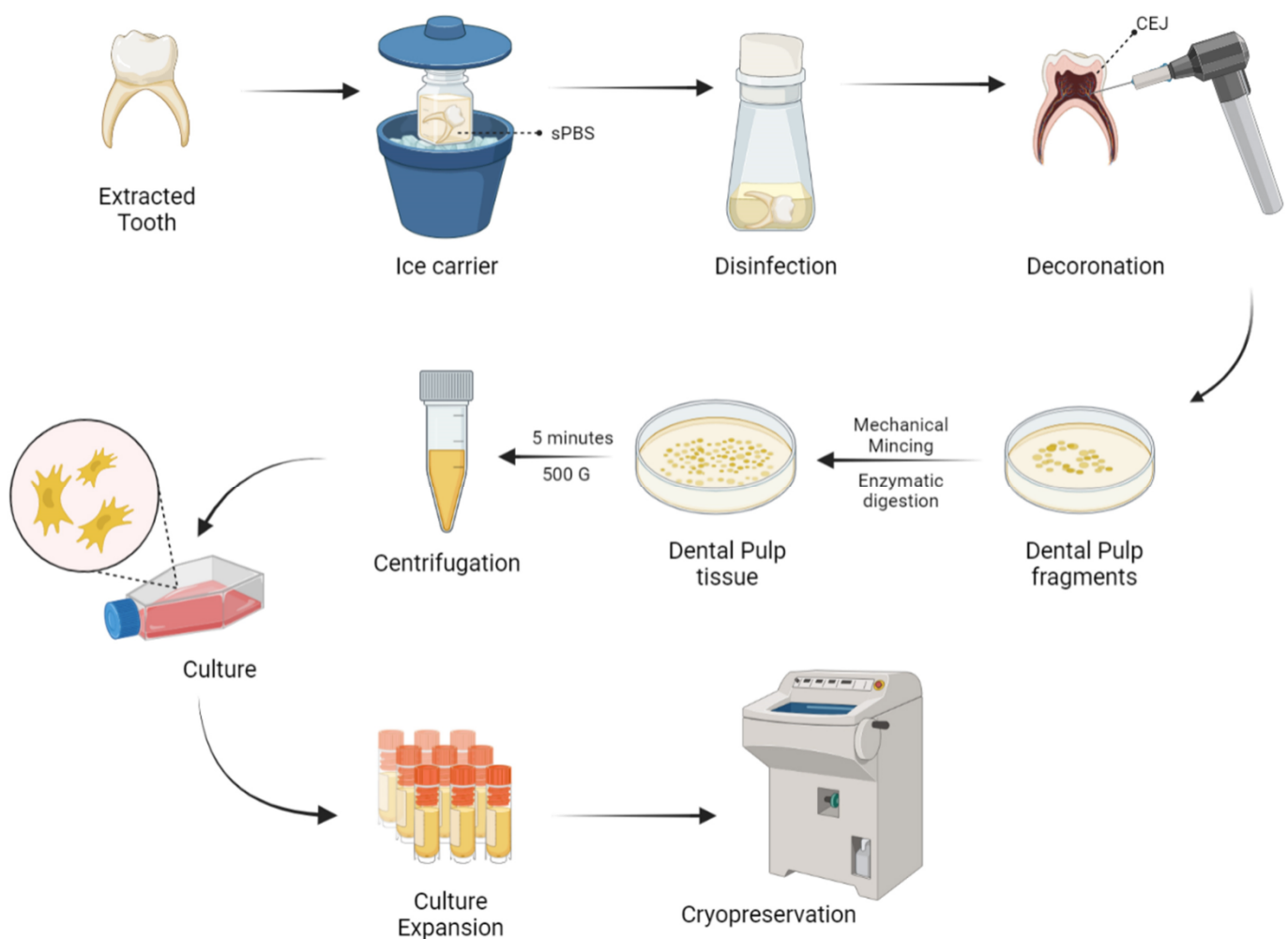


Figure 2. Harvesting and delivery method of DP-MSCs. sPBS—sterile phosphate buffer saline; CEJ—cementum enamel junction.

No significant change was observed in the differentiating capabilities and immunophenotypic properties of cryopreserved and non-cryopreserved DP-MSCs isolated from dental pulp, but there were significant differences in the morphology and proliferative potential of cryopreserved DP-MSCs than non-cryopreserved DP-MSCs [132].

The survival rates of DP-MSCs in DMSO free medium by static magnetic cryopreservation increased by 2 to 2.5 fold when the cells were exposed to 0.4 or 0.8-T static magnetic

fields [133]. Gioventù et al. demonstrated that cryopreserved teeth by laser piercing have maintained cellular viability [134].

To isolate a pure population of DP-MSCs, the identification of cell surface markers like LNGFR and THY-1 are significant [87,88]. The assessment of the number of colonies showed that LNGFR^{Low+}THY-1^{High+} cells in the dental pulp have a significantly higher colony-forming potential than LNGFR⁺THY-1⁺ cells in the bone marrow [135–137].

6. Chondrogenicity of Dental-Derived MSCs

Though dental-derived stem cells possess higher osteogenic potential, they are being explored very marginally for chondrogenicity. DP-MSCs act as a promising source for cartilage tissue engineering and regeneration. DP-MSCs possess a strong potential to differentiate into hyaline and fibrocartilage [138]. Sophia et al. demonstrated that hyaline cartilage contains few chondrocytes in their extracellular matrix rich in GAGs and type 2 collagen [2], whereas Allen et al. stated that fibrocartilage contains fibroblastic cells with small amounts of GAGs and type 1 collagen [139].

Longoni et al. expanded DP-MSCs from seven molar teeth and induced chondrogenesis in a 3D pellet culture system [63]. These culture-expanded DP-MSCs display GAGs, aggrecan, and type 2 collagen after three weeks. The assessment of culture-expanded cells revealed fibroblastic cells with long cytoplasmic processes with a predominance of type 1 collagen to state the formation of fibrocartilage. They concluded that DP-MSCs regenerate fibrocartilage in joints, rather than hyaline cartilage.

DP-MSCs provide a rapid ex-vivo expansion and chondrogenic differentiation potential and hence provide a favorable cell type for treating cartilage disorders. Khajeh et al. demonstrated a significant role of hypoxia mimicking agent and cobalt chloride on chondrogenesis with DP-MSCs [140]. Cobalt chloride exposure to DP-MSCs increases the cellular pellet mass in culture, cellular morphology and integrity, ECM deposition, and cellular organizations. There were elevated levels of GAGs and type 2 collagen expression [141]. Cobalt chloride enhances the stemness of DP-MSCs where flow cytometry reveals the increased expression of STRO-1⁺ cells [142].

SHEDs lose stemness and compromise the therapeutic effects when cultured and expanded in vitro for the long term. Hypoxia is a major factor in the maintenance of stemness of MSCs [143,144]. SHEDs, when co-cultured with cobalt chloride, increased the hypoxia-inducible factor-1 α in a dose-dependent manner, resulted in increased expression of STRO-1⁺ cells and stem/stromal cell markers such as OCT4, NANOG, SOX2, and c-Myc and decreased osteogenic differentiation by reducing ALP levels [141]. Hypoxia suppresses chondrogenic hypertrophy in agarose or alginate-chondroitin sulfate-platelet lysate hydrogel and 3D pellet culture system in cartilage tissue engineering [145,146]. At the protein level, the inhibitors of chondrocyte hypertrophy are PTHrP, TGF- β 3, BMP-4, -7, and -13, GG86/2, Dorsomorphin, and FK506, whereas, at the gene level, Nkx3.2, SOX-9, Smad6, HDAC4, ChM1, sFlt-1, and C-1-1 are responsible for inhibiting chondrocyte hypertrophy during culture [147–151]. The chondrogenesis due to hypoxia is mediated through SOX-9 gene transcription or p38 MAPK gene activation [152]. Hypoxia promotes chondrogenic differentiation and cartilage extracellular matrix synthesis and suppresses terminal chondrocyte differentiation and hence the hypoxia phenomenon preserves chondrocyte phenotype and function during chondrogenesis [153].

Hsu et al. cultured human gingival fibroblast (HGF) cells on chitosan membrane to observe in-vitro chondrogenesis. On culture, increased spheroid formation resulted, which indicates the stemness of HGF. Spheroid formation by HGF was supported by Rho/Rho-associated kinases and the connexin 43 pathway. Hence, they concluded that culturing HGF on chitosan membrane induces spheroid formation, which further induces chondrogenesis by the ROCK pathway [154].

Ferre et al. demonstrated osteogenesis and chondrogenesis by human gingival stem cells in vitro in 3D floating micromass pellet cultures in a specified medium. Osteogenic cells exhibited the increased expression of Runx-2, ALP, presence of osteoid-like mass, and

osterix expression whereas chondrogenic cells exhibited increased expression of type 2 collagen, GAGs, and SOX-9 transcription gene [155].

SOX-9, the master gene for chondrogenesis, helps in the proliferation of chondrocytes, but not in chondrocyte hypertrophy [156]. SOX-9 gene was expressed in human gingival stem cells at the basal level without chondrogenic stimulation [157]. Such basal expression of SOX-9 explains efficient chondrogenesis. SOX-9 gene knock-out mice were unable to regenerate normal cartilage despite MSC condensation [158–161]. The chondrogenesis by SOX-9 is due to

- (1) chondrocyte expression of SOX-9 until growth plate hypertrophy and in articular cartilage throughout life in adults,
- (2) to secure lineage specificity towards chondrogenesis in fetal and postnatal growth plates,
- (3) to maintain adult cartilage homeostasis,
- (4) and to repress non-chondrogenic lineages in gene level [115–117].

Ferre et al. demonstrated the differentiation of type 10 collagen secreting hypertrophic chondrocytes and fibroblast-like synoviocytes by human gingival stem cells. Under hypoxia and hypoxic mimicking environment, G-MSCs express high levels of VEGF- α , which promote vasculogenesis for regenerative therapies [155].

NOTCH ligand signaling plays a major role in the chondrogenic differentiation of cells [162]. NOTCH-2 modulates the activities of NOTCH-3 and -1, hence influence the growth and development, and homeostasis of chondrocytes and articular cartilage [163–165]. NOTCH-3 represses the proliferation of terminally differentiated chondrocytes within the cartilaginous tissues [166]. In a 3D-cultured chondrogenesis, there is a downregulation of NOTCH ligands and receptors [167,168]. While MSC undergoes terminal chondrocyte differentiation, NOTCH-3 receptors were upregulated and were highly expressed [162,169]. Various studies on the in vitro and in vivo chondrogenic potential of MSCs of dental origin are given in Tables 2 and 3, respectively.

Table 2. In-vitro chondrogenicity of MSCs of dental origin.

| Author | Objectives | Type of Scaffold | Chondrogenic Differentiation | Time Evaluation | Cell Passage | Growth Factor | Results |
|--------------------------------|--|---------------------------------|---|--------------------------------------|---------------|----------------|--|
| Fernandes et al. [170]. (2018) | Animal model for DP-MSCs for cartilage regeneration | Collagen type I/III | No | 6 weeks | Not described | No | Able to differentiate into bone and cartilage in-vitro |
| Westin et al. [171]. (2017) | Analyze the culture and differentiation of DP-MSCs into chondrocytes using scaffolds | Chitosan-xanthan gum matrices | DMEM supplemented with ascorbate, proline, ITS, dexamethasone, kartogenin | 24 h and 14 days after cells seeding | No | No | DP-MSCs seeded along with scaffolds differentiate into chondrocytes when cultured in chondrogenic medium containing kartogenin for 14 days |
| Mata et al. [172]. (2017) | Chondrogenic ability of hDP-MSCs to regenerate cartilage in vitro and in vivo | 3% alginate scaffold | DMEM with 1% insulin-transferrin-sodium selenite medium supplement and ascorbate | 3 months | Not described | No | By end of 3 months, a significant cartilage regeneration observed in rabbit model |
| Ishikawa et al. [173]. (2016) | Therapeutic benefits of SHED-CM for animal induced arthritis model | No | No | 14 days | 5–9 | No | Induction of M2 macrophage polarization and inhibition of osteoclastogenesis |
| Chen et al. [174]. (2014) | Chondrogenic potential of SHED with TCP scaffold in vitro and in vivo | β -tricalcium phosphate | Dexamethasone, insulin, ascorbate phosphate, TGF- β 3, bFGF, and 10% FBS. | 2, 4, and 8 weeks | 3 | No | SHED showed colony-forming capacity, odonto/osteogenic, and adipogenic differentiation capacity. |
| Rizk et al. [175]. (2013) | Cartilage-like constructs from DP-MSCs with TGF- β 3 transduction in vivo and in vitro | Poly-L-lactic acid/polyethylene | DMEM media with high glucose, insulin, bovine serum albumin, dexamethasone, ascorbate, and recombinant human TGF- β 3 | 7, 14, 30 days, and 12 weeks | 4 | TGF- β 3 | Transduced DP-MSCs highly expressed human TGF β 3 for up to 48 days and expressed chondrogenic markers |

Table 2. Cont.

| Author | Objectives | Type of Scaffold | Chondrogenic Differentiation | Time Evaluation | Cell Passage | Growth Factor | Results |
|------------------------------|---|---------------------------|--|-----------------|--|----------------|---|
| Hilkens et al. [176]. (2013) | Compare DP-MSCs isolated by enzymatic digestion with DP-MSCs using the explant method | No | D-MEM/F12 supplemented with 1% insulin transferrin selenite and chondrogenic supplement | 3 weeks | 2 and 4 | TGF- β 3 | DP-MSCs differentiate into osteogenic and chondrogenic lineages by both methods |
| Dai et al. [177]. (2012) | Costal chondrocyte s as a chondro-inductive niche for DP-MSCs in-vitro and in-vivo | Fibrous PGA | DMEM-F12 supplemented with 1% ITS, ascorbate-2-phosphate, proline, dexamethasone, TGF- β 3 | 8 weeks | P3 for DP-MSCs and P2 for chondrocytes | FGF9 | STRO-1+ DP-MSCs consist of several interrelated subpopulations, which can spontaneously differentiate into odontoblasts, osteoblasts, and chondrocytes. |
| Yu et al. [125]. (2010) | Differentiation potential of DP-MSCs at different passages | Absorbale gelatin sponges | No | P1 \times P9 | 1 and 9 | No | DPSCs at the 9th passage restrict their differentiation potential to the osteoblast lineage in vivo. |

Table 3. In-vivo chondrogenicity of MSCs of dental origin.

| Author | Animal model | Objectives | Type of Scaffold | Defect/Implantation | Time of Evaluation | Results |
|--------------------------------|---------------|--|---|-----------------------------------|------------------------------|--|
| Fernandes et al. [170]. (2018) | Miniature pig | Animal model for DP-MSCs for cartilage evaluation | Collagen type I/III | Knee/medial femoral condyle | 6 weeks | Animals tolerated the procedure well and did not show clinical or histological rejection of the DP-MSCs |
| Mata et al. [172]. (2017) | Rabbit | Chondrogenic ability of hDP-MSCs to regenerate cartilage in vitro and in vivo. | 3% alginate scaffold | Knee/trochlear groove | 3 months | Complete regeneration of cartilage was observed |
| Ishikawa et al. [173]. (2016) | Mouse | Therapeutic benefits of SHED-CM for an animal-induced arthritis model | No | No. Systemic osteoarthritis model | 14 days | SHED-CM inhibits osteoclast differentiation and subsequent bone destruction through direct and indirect mechanisms |
| Chen et al. [174]. (2014) | Rat | Chondrogenic potential of SHEDs with TCP scaffold in vitro and in vivo | β -tricalcium phosphate | Dorsal midline dermal space | 2, 4, and 8 weeks | After in vivo transplantation, SHED recombined with β -TCP scaffolds were able to generate new cartilage-like tissues. |
| Rizk et al. [175]. (2013) | Mice | Cartilage-like constructs from DP-MSCs with TGF- β 3 transduction in vivo and in vitro | Poly-L-lactic acid/polyethylene glycol (PLLA/PEG) | Back of nude mice | 7, 14, 30 days, and 12 weeks | Seeded on with scaffold, DP-MSCs formed 3D cartilage constructs in the area with cartilage defects. |
| Dai et al. [177]. (2012) | Mice | Costal chondrocyte s as chondro- inductive niche for DP-MSCs in vitro and in vivo | Fibrous polyglycolic acid (PGA) | Back of nude mice | 8 weeks | The differentiation capacity of DP-MSCs changes during cell passaging, and DPSCs at the 9th passage restrict their differentiation potential to the osteoblast lineage in vivo |
| Yu et al. [125]. (2010) | Rat | Differentiation potential of STRO-1 ⁺ DP-MSCs at different passages | Absorbable gelatin sponges | Renal capsule | 14 days posttransplantation | In vivo transplantation results showed that rat DPSC-P1 cell pellets developed into dentin, bone, and cartilage structures, respectively. |

7. Engineered Chondrogenesis by D-MSCs

Due to the intrinsic limited potential of cartilage tissue to heal, cartilage tissue engineering gave a robust breakthrough in the field of regenerative and translational medicine. The field of tissue engineering provides the biological substitute of limited available tissues to restore and maintain the naïve homeostasis and to improve the biomechanical strength and function of the tissues. The integral components of tissue engineering are stem/stromal cells, scaffolds, and bio-micromolecules [178–180]. The successfully engineered tissue relies on tissue ergonomics that include harvest and expansion of appropriate cells, the addition of optimum levels of growth factors and cytokines, and provision of 3D scaffold and extracellular matrices until the healing gets completed.

Growth factors: The cardinal growth factors responsible for cartilage engineering are TGF- β 1 and - β 3, BMP-2 and -7, IGF-1, and bFGF. TGF- β 1 induces and maintains chondrogenesis of MSC through chondrostimulatory signaling by p38, ERK-1, JNK, N-cadherin expression, and suppresses the IL-1 catabolism [181]. TGF- β 1 controls Wnt-mediated signaling and β -catenin TCF pathway in early MSC chondrogenesis [182]. TGF- β 3, when co-cultured with bovine MSCs in a chitosan scaffold, stimulates the growth of hyaline cartilage and integrates into the host cartilage [183]. BMPs are involved in Hedgehog and TGF- β signaling in regulating chondrogenesis both in vitro and in vivo [184–186]. BMP-2 inhibits IL-1 effects and enhances cartilage cell production by inducing chondrogenic factors, whereas BMP-7 enhances ECM production [187]. IGF-1 downregulates MMP-13 by upregulating collagen 2 expression and GAG synthesis [188]. IGF-1 induces in vitro and in vivo chondrogenesis in a dose- and time-dependent manner [189]. The evidence stated that bFGF-18 in a concentration-dependent manner stimulates and enhances chondrogenesis in the osteochondral lesion of rabbit knees [190,191].

Bioactive molecules: Kartogenin (KGN) enhances MSC chondrogenesis by upregulation of CBF β -RUNX1 transcription [192]. Evidence states that kartogenin promotes tendon and meniscus regeneration [193,194]. KGN inhibits pain stimulus, attenuates chondral degeneration and inflammation, supplements the biomechanical strength of repaired bones and tendons in-vivo animals, and robust chondrogenic differentiation of DP-MSCs [195]. Simvastatin, a hypolipidaemic molecule, enhances positive effects on synovium and cartilage tissues, thereby reducing inflammation, degeneration and halts arthritis progression [196]. A higher concentration of statins decreased the production of nitric oxide in chondrocytes and cartilage explants [197].

Bioactive scaffolds: Scaffolds, an integral part of tissue engineering, are of natural [collagen, fibrin, hyaluronan, alginate, agarose, and chitosan] and synthetic [polylactic acid (PLA), polyglycolic acid (PGA), and copolymer polylactic-co-glycolic acid (PLGA)] polymers. The ideal scaffold should be biocompatible, optimum porosity, biodegradable, elastic natured, mechanical strength, easy fabrication, non-toxic, long-term effectiveness, and support cell attachment and proliferation [198,199]. Platelet-rich plasma seeded with agarose enhance cartilage and tendon regeneration [200]. MSCs cocultured with collagen or agarose enhance chondrocyte differentiation along with increased production of ECM and GAGs [201]. Alginate, an injectable scaffold, is used in regenerating focal chondral defects and in autologous chondrocyte implantation [202,203]. DP-MSCs accelerate chondrogenesis when cultured with growth factors and alginate beads [204]. The synergistic effects of chitosan and hyaluronic acid hydrogel enhance the healing of cartilage defects in rabbits [205]. Synthetic polymer scaffolds are used in the repair of osteochondral defects in rabbits [206] and meniscal lesions in dogs [207].

Chondrocytes release factor FXIIIa, whose upregulation leads to hypertrophic chondrocyte differentiation in OA chondrocytes. In the murine OA cartilage model, there is an interplay between FXIIIa and α 1 subunit of α 1 β 1 integrin and tissue glutaminase 2 (TG2) mobilization, which leads to remodeling of the cartilage matrix. In absence of TG2, FXIIIa fails to undergo chondrocyte hypertrophy [208]. The conjunction of plasma membrane-bound TG2 and FXIIIa with a raised expression of FXIIIa upregulates the p38 MAP kinase signaling pathway in chondrocytes of OA cartilage in situ [209]. In turn, p38 signaling sig-

nificantly increases SOX-9, which inhibits both in vitro and in vivo chondrocyte maturation to hypertrophy by DP-MSC-induced chondrogenesis [210].

Cordycepin is a potent antioxidant molecule with anti-tumorigenic and anti-inflammatory properties [211]. During MSC-induced chondrogenesis, cordycepin upregulates type 2 collagen, SOX-9, and TGF- β 1 and - β 3 expression, whereas downregulates type 10 collagen and Runx-2 [162]. Cordycepin has the potential to construct engineered cartilage by the inhibition of chondrocyte hypertrophy through PI3K/Bapx1 and the westin signaling pathway [212]. Hence, cordycepin plays a major role in cartilage and chondrocyte metabolism.

DP-MSCs loaded onto nanostructured PEG-GELMA-HA hydrogel form 3D spheroids, which further differentiate into chondrocytes in vitro [61]. Scaffold-assisted chondrogenesis upregulates procollagen type 2 and 10, aggrecan, alkaline phosphatase, and SOX-9 genes and downregulates Nanog, Slug, Snail, and Twist genes [172,213]. IHC analysis exhibit type 2 collagen deposition in DP-MSCs co-cultured with PEG-GELMA-HA hydrogel scaffold. These findings direct the usage of DP-MSCs to construct engineered cartilage in focal cartilage and osteochondral defects.

Expanded chondrocytes from MSCs co-cultured with PGA-fibrin scaffolds revealed considerable expression of type 1 and 2 collagen and further resulted in the formation of hyaline cartilage. Upon optimal addition of platelet-rich plasma to cartilage tissue, the formation of hyaline cartilage was robust with higher expression of collagen type 2 [214].

Loading of human dedifferentiated chondrocytes into collagen sponge, in the presence of hypoxia and BMP-2, resulted in chondrogenesis, which is transfected onto siRNAs targeting collagen type 1 and HtrA1 serine protease, which are raised in OA cartilage. Such a mechanism led to the improvement of chondrocyte phenotype differentiation. Transplantation of in vitro cultured cells into nude mouse model in vivo resulted in neochondrogenesis with hyaline matrix formation [215]. The in vitro and in vivo studies on cartilage tissue engineering using stem cells of dental origin are tabulated in Tables 4 and 5.

Table 4. In vitro studies on cartilage tissue engineering using stem cells of dental origin.

| Author | Methods | Main Results |
|--------------------------------|--|---|
| Fernandes et al. [170]. (2018) | Transmission electron microscopy | MSCs derived from dental pulp had intact membranes and scattered microvilli-like structures on their surfaces, showing good attachment to the biomaterial scaffold. |
| Westin et al. [171]. (2017) | Indirect toxicity of scaffolds to DP-MSCs | Biomaterial produced is not capable of affecting the growth of DP-MSCs |
| | Histology | The formation of collagen fibers by DP-MSCs in culture can be observed, confirming that DP-MSCs were able to effectively differentiate into chondrocytes within the cultured matrix |
| Mata et al. [172]. (2017) | Chondrocyte differentiation | Chondrocytes and hDP-MSCs grown in chondral differentiation medium showed a rounded morphology that correlated with significant expression of COLII and ACAN. |
| Ishikawa et al. [173]. (2016) | Evaluation of SHED-CM potential for inhibition of osteoclastogenesis and M2 macrophage induction | BMCs cultured in SHED-CM underwent reduced osteoclast differentiation; Increased number of CD206 ⁺ macrophages with upregulation of CD206 and arginase genes in SHED-CM |
| Chen et al. [174]. (2014) | Chondrogenic differentiation of SHED | Confirmation of chondrogenic differentiation of SHED by toluidine blue staining, safranin O staining, type II collagen, and aggrecan immunostaining |
| | SHED and TCP analysis by scanning electron microscopy | Rich ECM was secreted by SHED on day 7 with TCP |

Table 4. Cont.

| Author | Methods | Main Results |
|--------------------------------|---|---|
| Fernandes et al. [170]. (2018) | Transmission electron microscopy | MSCs derived from dental pulp had intact membranes and scattered microvilli-like structures on their surfaces, showing good attachment to the biomaterial scaffold. |
| Rizk et al. [175]. (2013) | Cytologic evaluation of DP-MSCs in vitro | TGF- β 3-transduced DP-MSCs formed well-defined micro masses |
| | DP-MSCs and scaffolds in vitro by scanning electron microscopy | Increases in type IIA collagen, aggrecan, and SOX-9 in both TGF- β 3- transduced DP-MSCs and those supplied with TGF- β 3. |
| Hilkens et al. [176]. (2013) | Morphology | Heterogeneous cell culture |
| | Immunophenotype, proliferation rate, adipogenic, osteogenic, and chondrogenic differentiation | Immunophenotype, proliferation rate, and adipogenic, osteogenic, or chondrogenic differentiation showed no significant difference between groups |
| Dai et al. [177]. (2012) | In vitro analysis | Cultured chondrocytes enhance the expression of SOX-9, ACAN, and COL2 and downregulate the expression of the early hypertrophic marker COL10 |
| | Markers in DP-MSCs in response to FGF9 or CM. | Intense FGFR3 staining and strong phosphorylation of ERK1/2 staining in monolayer DP-MSCs cultured in CM with FGF9. |
| Yu et al. [125]. (2010) | In vitro analysis | DP-MSCs differentiation markers showed significant upregulation in the 9th passage. |

Table 5. In vivo studies on cartilage tissue engineering using stem cells of dental origin.

| Author | Methods | Main Results |
|--------------------------------|---|--|
| Fernandes et al. [170]. (2019) | Macroscopic and histological evaluation | Scaffolds plus DP-MSCs showed coverage of the defect and new tissue growth over the cartilage. Scaffold alone showed a regular defect border and shallow tissue coverage over the defect. |
| Mata et al. [172]. (2017) | Macroscopic evaluation | The loss of cartilage was diminished in animals implanted with alginate containing either chondrocytes or hDP-MSCs. |
| | Immunochemistry | Higher expression of type II collagen with no significant expression of type I collagen in groups with chondrocytes and hDP-MSCs. |
| Ishikawa et al. [173]. (2016) | Clinical finding—Edema | SHED-CM-treated mice exhibited minimal paw swelling, while DMEM- and BMSC-CM-treated mice displayed severe and moderate swelling encompassing the ankle, foot, and digits |
| | Histological evaluation | Quantitative histological scores of synovial inflammation, bone erosion, and cartilage damage were all significantly lower in SHED-CM-treated mice than in the BMSC-CM- or DMEM-treated mice |
| | Immunohistochemistry | SHED-CM and BMSC-CM groups reduced the proportion of iNOS+F4/80+ M1 cells, and the proportion of CD206+F4/80+ M2 cells was increased in the SHED-CM group, but not the BMSC-CM group. |

Table 5. Cont.

| Author | Methods | Main Results |
|---------------------------|---|---|
| Chen et al. [174]. (2014) | Histological evaluation | SHED produces rich ECM on day 7 with β -tricalcium phosphate |
| | Immunohistochemistry | Cartilage-like tissue stained positive for type II collagen |
| Rizk et al. [175]. (2013) | Western blot analysis | Expression of collagen II, Sox9, and aggrecan in constructs seeded with TGF- β 3- transduced cells |
| | RT-PCR | TGF- β 3-transduced DP-MSCs exhibited an increased expression of collagen II |
| Dai et al. [177]. (2012) | Histological evaluation of cellular morphology and GAG quantification | Co-cultured DP-MSCs with cultured chondrocyte transplants were larger and had increased cartilaginous matrix deposition and higher GAG quantification |
| Yu et al. [125]. (2010) | Histology evaluation of STRO1+DP-MSCs in transplanted P1 and P9 pellets | Eat DP-MSC- P1 cell pellets developed into dentin, bone, and cartilage structures, while DP-MSC-P9 cells could only generate bone tissues. |

8. Future Perspectives

The U.S. Army has invested over \$250 million towards stem cell research to aid in the management of their injured soldiers in the field through a project called Armed Forces Institute for Regenerative Medicine. In recognition of the regenerative potential of dental stem cells, a trend towards establishing tooth banks is on the rise in developed and developing countries [216–219]. More research is directed towards their application in cardiac ailments [220], regenerating brain tissue [221], muscular dystrophy [222], and bone regeneration [223]. With the pursuit towards their regenerative potential, future clinical studies are needed to validate the results of various animal model and in vitro studies to prove the concept of chondrogenic differentiation of the implanted MSCs of dental origin to be of use in various common clinical conditions such as osteoarthritis that leads to cartilage degeneration.

9. Conclusions

MSC-based therapies are the upcoming biological modality of management of various ailments in the current decade. Having discussed the potential of the various dental-derived stem cells towards various regenerative domains including dental pulp stem cells towards chondrogenesis, their potential for future utility in mitigating various pathomechanisms and restoring the normal homeostasis needs further exploration. Future clinical studies are needed to evaluate their effectiveness in varied clinical scenarios to enable practical utility. With the evolution of the understanding of these cell-based regenerative therapies, dental tissue-derived cells would prove to be a more promising tool in the management of various diseases and help in the further advancement of medicine in the future.

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