International Journal of Nanomedicine

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REVIEW

Nanomaterials Modulating the Fate of Dental-Derived Mesenchymal Stem Cells Involved in Oral Tissue Reconstruction: A Systematic Review

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Abstract: The critical challenges in repairing oral soft and hard tissue defects are infection control and the recovery of functions. Compared to conventional tissue regeneration methods, nano-bioactive materials have become the optimal materials with excellent physicochemical properties and biocompatibility. Dental-derived mesenchymal stem cells (DMSCs) are a particular type of mesenchymal stromal cells (MSCs) with great potential in tissue regeneration and differentiation. This paper presents a review of the application of various nano-bioactive materials for the induction of differentiation of DMSCs in oral and maxillofacial restorations in recent years, outlining the characteristics of DMSCs, detailing the biological regulatory effects of various nano-materials on stem cells and summarizing the material-induced differentiation of DMSCs into multiple types of tissue-induced regeneration strategies. Nanomaterials are different and complementary to each other. These studies are helpful for the development of new nanoscientific research technology and the clinical transformation of tissue reconstruction technology and provide a theoretical basis for the application of nanomaterial-modified dental implants. We extensively searched for papers related to tissue engineering bioactive constructs based on MSCs and nanomaterials in the databases of PubMed, Medline, and Google Scholar, using keywords such as "mesenchymal stem cells", "nanotechnology", "biomaterials", "dentistry" and "tissue regeneration". From 2013 to 2023, we selected approximately 150 articles that align with our philosophy.

Keywords: nano-material, stem cell, tissue reconstruction, cell differentiation

Introduction

Trauma, tumor, infection, and congenital malformation can cause soft and hard tissue defects in the oral and maxillofacial region, thus impairing facial aesthetics, physical function, and social communication ability and seriously affecting patients' physiological and psychological health and social status.[1] However, due to the complex three-dimensional anatomical structure, various tissue layers, and the tendency to form scar healing, it is not easy to repair completely and regain function with existing repair methods such as flap transfer repair.[2,3] Exogenous bone replacement materials are prone to disease transmission and immune reactions, and artificial material grafts are challenging to obtain ideal therapeutic results due to the lack of osteogenic induction characteristics.[4] Autologous bone grafting was once considered the gold standard for bone filling, but donor shortages and complications have limited its development.[3] With the advancement of tissue engineering technology and stem cell research, various bioactive materials and odontogenic stem cells have received widespread attention and have been gradually applied in clinical practice.

Received: 27 April 2023
Accepted: 3 September 2023
Published: 21 September 2023

Bioactive nanomaterials are specialized biomaterials used at the nanoscale to obtain better therapeutic efficacy than conventional inert materials by inducing bioactive reactions or modulating biological functions.[5] Various natural and artificial materials have ideal avenues of application in nanomaterials. Their unique nano-size effect and bioactive efficacy resulting from their interaction with the organism allow for biomedical applications such as bone tissue engineering, drug delivery, and wound dressings.[5–7] In oral and maxillofacial soft and complex tissue defect repair, nano-bioactive materials can be obtained from a wide range of sources with significant bioefficacy. They can mimic the natural process of embryonic development by guiding the formation of functional tissues and organs from undifferentiated mesenchymal stem cells, thus reducing the occurrence of immune reactions.[8]

DMSCs have biological properties such as self-renewal, multidirectional differentiation, and high growth potential. They can proliferate, homogenize, and differentiate under the guidance of cytokines and scaffolding materials to achieve tissue transformation, which includes dental pulp stem cells (DPSCs),[9] stem cells from human exfoliated deciduous teeth (SHEDs),[10] and periodontal membrane stem cells (PDLSCs)[11], root apical papillary stem cells (SCAPs),[12] and dental follicular stem cells (DFSCs),[13] which have received widespread attention for their wide variety of differentiable cells,[14–17] long in vitro storage time,[18,19] and good interaction with scaffolds and growth factors.[20–22]

Notably, the repair effect mediated by MSCs depends on the modulation of the bionic microenvironment established by tissues and biomimetic materials;[23,24] in addition to the fibrous structure of nanomaterials, which has been shown to mimic the design of the extracellular matrix (ECM), thereby inducing the adhesion, proliferation, and differentiation of MSCs,[25] some of the nanomaterials, such as calcium phosphates, can induce the remineralization capacity of MSCs by mediating the release of Ca and P ions by the release of Ca and P ions from functional groups to activate the remineralization ability of MSCs;[26] nanofibrous sponge microspheres made of l-lactic acid can also induce up-regulation of vascular endothelial growth factor (VEGF) genes through hypoxia to enhance the vasculogenic ability of MSCs.[27] Graphene-based materials can also stimulate the osteogenic differentiation of MSCs by increasing the osteoinductive conductivity.[28] More and more studies have demonstrated the great relevance of nanomaterials to cell growth and development, metabolism, differentiation, and immunomodulation.[29–31]

In addition, nanomaterials are gradually gaining prominence for applications in dental caries, endodontic diseases, periodontal diseases, and intraoral implants. Silver nanoparticles (AgNPs) and zinc nanoparticles (ZnNPs), which do not form oxides when they come into contact with oxygen in the oral environment, have enhanced biocompatibility and antimicrobial properties and are more suitable for the prevention and treatment of dental caries than conventional materials.[32–34] Several studies have shown that the antimicrobial effect of AgNPs is also suitable for root canal disinfection.[35,36] A multifunctional material based on the nano-Si /Ca(Sr) system has been developed, which achieves acid resistance, bacterial inhibition, low cytotoxicity, and promotes dentin biomimetic remineralization, which can reduce dentin hypersensitivity.[37] Nanomaterials are also increasingly used in periodontitis diagnosis, treatment, and tissue engineering, not only developing magnetic nanoparticle-based sensors for a comprehensive assessment of periodontitis, but also drug delivery in the form of nanoparticles, nanocapsules, and nanofibers, and modulation of stem cells using nanocomposite scaffolds as carriers.[38] Nanoengineering, which is a new platform to enhance the bioactivity of dental implants, has been used to enhance the antimicrobial and bioactive properties of conventional implants and improve the long-term therapeutic outcome by fabricating titanium dioxide nanotubes (TNT), nanoparticles (NPs), and various types of biopolymers through physical modification, chemical modification, mechanical modification, and biomolecular modification.[39]

In summary, nanomaterials modulating the fate of MSCs have become a hot research topic in tissue repair and regeneration, and the modulation of different MSCs by different materials is also a topic worthy of investigation, so this paper outlines the latest developments in the fabrication of implantable biomaterials with nanostructures and evaluates them.

Dental-Derived Mesenchymal Stem Cells

Please refer to Figure 1[40] and Table 1.

DPSC

As an essential component of odontogenic MSCs, DPSCs have a unique position in repairing maxillofacial injuries in the body under their high differentiation characteristics and ability to regenerate the dentin/pulp complex. In 2000, Gronthos

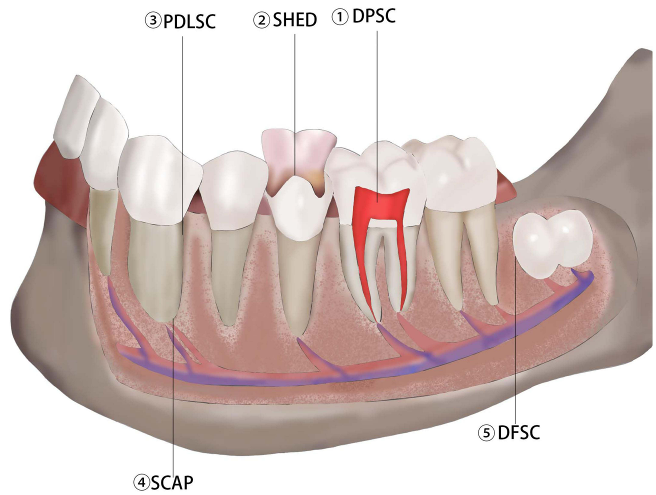

Figure 1 The origin of DMSCs.

Notes: Dental pulp stem cells (DPSC). Mostly derived from healthy milk teeth and wisdom teeth, they have the potential for multidirectional differentiation. In addition to the ability to form mineralized nodule-capable cells, they can also differentiate into cell lineage types such as adipose, bone, cartilage, muscle, vascular endothelium, hepatic, and neural cell types after induction by different cytokines. The main advantages include abundant sources, side effects, and no ethical controversies. Human mammary dental stem cells (SHED). Most of the tissues are extracted from the healthy milk teeth of the affected children, with multi-directional differentiation potentials such as osteogenic differentiation, lipogenic differentiation, and differentiation in the direction of neuronal cells. Periodontal stem cells (PDLSC). PDLSCs are derived from normal human dental tissues and express Stro-1, a marker of MSCs, and have multidirectional differentiation potential. Stem cells of the apical papilla (SCAP). SCAPs are primarily developed from the apical part of young permanent teeth with immature roots and secrete exosomes that play an essential role in the repair of tissue damage, organ development, and immunomodulation of the body. Dental Follicular Stem Cells (DFSC). Derived from the cranial neural crest, DFSCs are mesenchymal precursor cells around the dental embryo that form osteoid, periodontium, and alveolar bone during tooth development. Adapted from Chalisserry EP, Nam SY, Park SH, Anil S. Therapeutic potential of dental stem cells. *J Tissue Eng*. 2017;8. Creative Commons and with Permission of SAGE Publications.[40]

et al isolated a type of fibroblast with a multidirectional differentiation potential and named it dental pulp stem cells while studying dental pulp tissues.[9] As neural crest-derived cells, DPSCs can be used for cell therapy along several cell lineages.[51] Currently, many studies have demonstrated the ability of DPSCs in neural differentiation, angiogenesis, dentinogenesis, osteogenesis, and chondrogenesis,[41,42,52–56] not only in the maxillofacial region but also in tissues throughout the body (eg, the brain, heart, cornea). Recently, their secreted factors have shown therapeutic potential in various diseases.[41,42] The differentiation process is often influenced by the scaffolds and growth factors used, eg, embedded collagen/chitosan scaffolds promote dentin differentiation of DPSCs,[52] a bioengineered scaffold provided by porcine decellularized dental pulp has also been found to have a pro-dentin/enamel differentiation effect,[53]

Table 1 Classification and Research Progress of DMSCs

Cell	Induction Direction	Example	Reference
DPSC	Odontogenic differentiation	Embedded collagen/chitosan scaffold promotes dentinogenic differentiation of DPSCs.	Zhang W et al/2017[41]
DPSC	Odontogenic differentiation	A bioengineered scaffold provided by porcine decellularized dental pulp also had a pro-dentin/enamel differentiation effect.	Hu L et al/2017[42]
SHED	Osteogenic differentiation	Incorporating SHEDs into gelatin/bioactive glass (GEL/BGM), scaffolds were found to repair bone defects and promote new bone formation significantly.	Xiong H et al/2022[43]
SHED	Osteogenic differentiation	A significant increase in ALP concentration and osteogenic potential was observed in SHED induced on gHA scaffold.	Hagar MN et al/2021[44]
PDLSC	Osteogenic differentiation	Activation of the autophagy pathway by up-regulation of β-microtubulin III and down-regulation of chelator 1 / p62 thereby enhancing osteogenesis in PDLSCs slices	Zhang Y et al/2021[45]

(*Continued*)

Table 1 (Continued).

Cell	Induction Direction	Example	Reference
PDLSC	Neurogenic differentiation	It can differentiate into neurogenic cells and recruit endogenous neural stem cells at the injury site.	Mohebichamkhorami F et al/2022[46]
PDLSC	Osteogenic differentiation	Receiving osteogenic induction by affecting the KEGG pathway	Kwack KH et al/2022[47]
SCAP	Osteogenic differentiation	Berberine (BBR) stimulates the Wnt/β-catenin pathway and induces osteogenic differentiation of SCAPs.	Cui Y et al/2020[48]
SCAP	Neurogenic and vasculogenic differentiation	Further evidence of the potential for neural differentiation and angiogenic differentiation of SCAPs through induction of biological potential	Liu J et al/2022[49]
DFSC	Osteogenic differentiation	Co-culture of HUVECs with DFSCs revealed that their secreted angiogenic factors stimulated osteogenic differentiation of DFSCs	Bok JS et al /2018[50]

transforming growth factor (TGF-β) enhances the proliferation and chondrogenic differentiation of DPSCs,[55] and *nerve growth factor (NGF)* affects the neurogenic ability of DPSCs.[56] The excellent proliferation and differentiation ability of DPSCs protects patients in maxillofacial restoration and provides more possibilities for stem cell research in the biomedical field.

SHED

Miura M et al found that human deciduous teeth contain highly proliferative clonal cells known as SHEDs.[57] Originating from perivascular neuronal cells and neuroglia, SHEDs have strong angiogenic, neurogenic, and odontogenic differentiation abilities and have great potential in the repair of oral pulp tissues.[58] Xiong H et al incorporated SHEDs into gelatin/bioactive glass (GEL/BGM) scaffolds and found that they could significantly repair bone defects and promote the formation of new bone.[43] Similarly, Hagar MN et al induced osteogenesis of SHEDs on granular hydroxyapatite scaffolds (gHA) and found that alkaline phosphatase (ALP) concentration was significantly increased, and osteogenic potential was enhanced considerably.[44]

Compared with other mesenchymal cells, such as DPSCs and bone marrow mesenchymal stem cells (BMSCs), SHEDs have superior proliferative capacity and faster colony formation efficiency. In addition to dental pulp regeneration, in recent years, SHEDs have made significant progress in neurological research. Some studies have reported that SHEDs can not only alleviate trigeminal neuralgia by inhibiting endoplasmic reticulum stress but also prevent apoptosis of neural progenitor cells to a certain extent and promote facial nerve regeneration.[59,60] Although the proliferation and differentiation of SHEDs share similarities with many odontogenic MSCs, their natural shedding and non-invasive acquisition add new possibilities for stem cell applications, and storing SHEDs when children shed their milk teeth may be beneficial in treating future injuries or diseases.[59,61–65]

PDLSC

Since the first extraction of PDLSCs from periodontal membranes by Seo BM,[11] research on the differentiation of this cell has been a hot topic. More and more researchers have discovered its excellent differentiation potential to be able to differentiate into many types of mesenchymal lineage cells, such as osteoblasts, chondrocytes, cementoblasts, and adipocytes in vitro, and to regenerate PDL-like tissues in vivo.[46,47,66] Zhang Y et al found that gold nanoparticles (AuNPs) activated the autophagy pathway by upregulating β-microtubulin III and down-regulating chelator 1 / p62, enhancing osteogenesis in PDLSCs slices.[45] Li X et al, on the other hand, noted that the reactive oxygen species (ROS) encapsulated in menaquinone (MitoQ; an autophagy enhancer) released the nanoparticle, released menaquinone effectively induced mitochondrial autophagy via the *PINK1-Parkin* pathway and successfully reduced oxidative stress by decreasing the number of reactive oxygen species, which was beneficial for periodontal regeneration.[67] The study of PDLSCs exosomes (PDLSCs-Exos) has also been gradually increasing. FOR THE FIRST TIME, Liu T et al revealed that miRNAs originating from PDLSCs-Exos might promote the osteogenic differentiation of BMSCs.[68] Liu M et al found that PDLSCs-Exos could also alleviate high glucose-induced senescence in PDLSCs by transferring miR-3-1p to activate the *KEAP2-NRF* signaling pathway.[69] More and more studies have shown that the cell fate of PDLSCs is capable of targeted regulation and that epigenetic modifications, endoplasmic reticulum-mitochondrial coupling, and diabetic metabolites have inhibitory effects on osteogenic differentiation of periodontal stem cells,[70–72] which undoubtedly provides significant value for stem cell transplantation therapy.

SCAP

Stem cells derived from the apical papillae of immature permanent teeth (SCAPs), since Huang GT discovered that SACPs could differentiate into pulp tissue,[73] Bakopoulou A and Han C et al explored their differentiation and proliferation potentials respectively. Surprisingly, SCAPs were superior to DPSCs in differentiation ability and to PDLSCs in proliferation ability which makes SCAPs a promising candidate for periodontal tissue regeneration.[48,49,74–76] Wu X et al, on the other hand, co-cultured DFSCs with SCAPs and found that the osteogenic and fibrotic abilities of DFSCs were inhibited, suggesting that SCAPs regulate the fate of DFSCs.[77] Hilkens P et al, on the other hand, found that transplantation of SCAPs-containing of 3D-printed hydroxyapatite scaffolds resulted in the successful formation of vascularized dentin/pulp-like tissues, opening up a new frontier in the field of dental tissue engineering.[78]

DFSC

DFSCs are derived from a loose connective tissue capsule with specific markers of MSCs, such as *Nestin, stromal cell antigen 1 (Stro-1), CD105, and CD90*, and have been shown in recent years to have similar cell stemness to DPSCs and PDLSCs. Rezai-Rad M et al demonstrated the osteogenic potential of DFSCs;[79] Bok JS et al co-cultured human umbilical vein endothelial cells (HUVECs) with DFSCs and found that their secretion of angiogenic factors stimulated the osteogenic differentiation of DFSCs.[50] Rezai-Rad M et al demonstrated that DFSCs could repair craniofacial defects and that PCL could be used as a scaffolding material implanted into DFSCs for bone regeneration.[79] However, more studies on the co-culture of bioactive nanomaterials with such cells are, and their interaction has yet to be proved.

Modulation of Tooth-Derived Stem Cells by Various Materials

Please refer to Table 2.

Natural Materials (Alginate, Chitosan)

In today‘s rapidly evolving biomedical field, natural materials have been gradually developed for biomimetic scaffolds, drug delivery, and tissue repair. They have been extensively utilized for their wide range of sources and biocompatibility.[118] In recent years, more and more cases of natural materials have been reported for dental biomaterials. The study of natural materials at the nanoscale has promoted interdisciplinary academic exchanges, with natural polysaccharides, such as chitosan and alginate, being the most popular materials for current research.[119,120]

Alginate-Based Materials

Alginate is an unbranched polysaccharide composed of β-D-mannuronic acid and its C-5 differential isomer α-L-guluronic acid,[121] a salt derivative of alginate. As a natural polymer, alginate has excellent biocompatibility and plasticity, implying that the solubility, hydrophilicity, viscosity tunability, and mechanical properties of alginate can be adjusted to different degrees under different modifications, making it a promising biomaterial.[122] Nano-spongy alginate scaffolds obtained by freeze-drying technique have high porosity and interconnectivity,[123] which can provide sufficient sites for cells to use for their survival and growth, and have different effects on the growth and differentiation of tooth-derived MSCs when modified with other materials. Silvia Sancilio et al showed that alginate mixed with hydroxyapatite in water to form a composite scaffold using the calcium release method (ALg/HA) modulated *cyclooxygenase 2 (COX2) and prostaglandin E2 (PGE2)* expression of dental pulp stem cells and, in line with the trend of biocompatibility of this

Table 2 Effect of Nanomaterials on DMSCs

Material	Characterization	Cell Type	Concentration	Results	Conclusion	Reference
E-caprolactone embedded alginate with different nanohydroxyapatite contents.	The porous spongy and porosity of the samples decreased from about 81.8% to about 68.05% as the n-HA content increased from 10% to 30%.	DPSC		Increased cellular activity; Cellular BGLAP, BMP2, and RUNX2 gene expression was significantly increased	Promotes cell proliferation; promotes osteogenic differentiation of cells	Hokmabad VR et al/ 2019[80]
Structure of alginate/ gelatin/nano-hydroxyapatite (ALg/ Gel/nHA) microcapsules	Rougher and denser surface morphology	DPSC		Increased cellular activity; Increased cellular osteocalcin, BMP2, RunX2, osteonectin, and DSPP expression; increased ALP activity	Cell adhesion is more enhanced, proliferation is good, and cell osteogenic differentiation is promoted	Alipour M et al/2021[81]
Novel nanomaterials of hyaluronic acid/ alginate	The porous morphology pore sizes ranged from 45 μm to 89 μm. A slight increase in porosity was observed by increasing the proportion of hyaluronic acid in the hydrogel mixture	PDLSC		Cellular activity was increased; β-NGF release was prolonged with increasing HA concentration; increased cellular βIII-tubulin and GFAP expression	Promotes cell proliferation and cellular neurogenic differentiation	Ansari S et al/2017[82]
Nano-apatite and carboxymethyl chitosan composite scaffolds for biomineralization	Highly interconnected porous microstructures, while chemical characterization revealed specific functional groups for HAnp and CMC	DPSC	1:5 HAnp-CMC	Increased cellular activity Increased expression of DSPP, VEGF	Promote cell proliferation and DPSC osteogenic and angiogenic differentiation	Baskar K et al/2022[83]
Nano-apatite and carboxymethyl chitosan composite scaffolds for biomineralization	Porous microstructure with pore sizes ranging from 60 μm-200 μm and a molar ratio of 1.67 Ca/P, both HAp and CMC with characteristic functional groups	DPSC	1:5 w/w	Increased cellular activity; Increased expression of OPN, VEGF, and DSPP; Increased ALP activity	Promotes cell proliferation; promotes osteogenic and vascular differentiation of cells	Gurucharan I et al/ 2022[84]
Chitosan scaffolds containing Ca-SAPO (aluminum silicate phosphate)-34 and Fe-Ca-SAPO-34	SAPO-34 combined with nanoparticles resulted in a smaller pore size. In this study, the average pore size of the porous scaffolds was 145 ~ 180 μm	PDLSC	10% SAPO-34/chitosan	Increased cellular activity; Increased ALP activity; Increased expression of BGLAP, BMP-2, RUNX-2, SPARC	Promotes cell proliferation; promotes osteogenic differentiation of cells and correlates with Ca and Fe content	Navidi G et al/2021[85]

Chitosan fiber scaffolds with added Sr elements	The chitosan scaffolds were 8 mm in diameter and 6 mm in height. The scaffolds had a uniform structure and regular porosity, with a pore diameter of about 150 µm and well-interconnected pores	SCAP, SHED		Increased cellular activity; Increased expression of Collagen type1, Osteinectin, Osteocalcin; Increased ALP activity	Promotes cell proliferation; promotes osteogenic differentiation of cells	Su WT et al/2014[86]
Nano-hydroxyapatite (n-HAp)		DPSC		Increased expression of ALP, OPN, RUNX1, OCN, and collagen genes	Promoting cellular odontogenic differentiation	Hanafy AK et al/2018[87]
Alginate/ hydroxyapatite (Alg/ HAp) composite scaffolds		DPSC	2% (*w/v*)	Increased ALP activity; Increased type I collagen release; Increased expression of RUNX2, SP7, BMP2	Promotes osteogenic differentiation of cells	Sancilio S et al/2018[88]
Boron-modified bioactive glass	The thickness of the asymmetric 7B - BG-containing bilayer is about 195 µm, of which about 50 µm thick is a dense (solvent casting) layer and about 145 µm thick is a porous (electrospinning) layer	DPSC	7% SiO2	Increased cell viability; Increased ATPase activity	Promotes cell proliferation; promotes osteogenic differentiation of cells	Moonesi Rad R et al/ 2019[89]
Cu-doped bioactive glass nanospheres	Spherical mesoporous nanospheres	DPSC		Increased cell viability; Increased expression of COL1A, DMP-1, DSPP, OCN	Promotes cell proliferation; promotes osteogenic and odontogenic differentiation of cells	El-Fiqi A et al/2020[90]
Mesoporous bioactive glass nanoparticles (MBN/ GO) composites	Spherical with a diameter in the range of 300–600 nm.	DPSC	MBN/GO (40:1 and 20:1) composites	Increased cell viability; Increased expression of DSPP, DMP-1, RUNX-2, BMP-2, ALP and MEPE	Promotes cell proliferation; promotes cell osteogenesis	Ahn JH et al/2020[91]
Polyhydroxybutyrate (PHB)/chitosan/nano-bio glass (nBG) nanofiber scaffolds		SHED		Increased cell viability; Increased ALP activity; Increased expression of DSPP and type I collagen	Promotes cell proliferation; promotes cell osteogenesis	Khoroushi M et al/ 2020[92]
Polycaprolactone (PCL)-Poly(ethylene oxide) (PEO) blends		DPSC		Increased expression of RUNX-2, type I collagen, osteonectin and OSC genes	Promote cellular osteogenesis	Hosseini FS et al/2019[93]

(*Continued*)

Table 2 (Continued).

Material	Characterization	Cell Type	Concentration	Results	Conclusion	Reference
Berberine/polycaprolactone/collagen (BBR/PCL/COL) scaffolds	The scaffolds all have a disordered fiber structure, and the average fiber diameter decreases with the increase of BBR content	DPSC	Scaffolds containing 50 µg/mL BBR	Increased expression of ALP, BMP2, OCN, COL-1	Promote cellular osteogenesis	Ma L et al/2021[94]
Poly (e-caprolactone)-poly(ethylene glycol)-poly(e-caprolactone) (PCL-PEG-PCL / zeolite nanofibers)	Beadless structures with an average diameter of 437 nm	DPSC		OCN, BMP 2, and RUNX 2 expression increased; No significant change in DSPP expression	Promotes cell growth and proliferation; promotes cell osteogenesis; hardly promotes cell dentition	Alipour M et al/2019[95]
PCL/*Elaeagnus angustifolia* extract (nHAEA)	Nanofiber diameter 191.8 ± 43.1 nm, 85° contact angle	DPSC	PCL polymer (10% wt) was dissolved in acetic acid (90%) and nHAEA (20% wt) was added to the PCL solution	Increased cell viability; Increased expression of BMP2, RUNX2 and DSPP	Increased cell viability; Increased expression of BMP2, RUNX2 and DSPP	Azaryan E et al/2022[96]
Polyvinyl alcohol (PVA)-polycaprolactone (PCL) bioceramic (HAB) electrostatically spun composite scaffolds		DPSC		Increased ALP activity; Increased osteoblast gene expression; Increased ability to form mineralized matrix	Promotes osteogenic differentiation of cells	Prabha RD et al/2018[97]
Addition of strontium phosphate to polycaprolactones		SHED		Increased ALP activity; Increased osteoblast gene expression	Promotes osteogenic differentiation of cells	Su WT et al/2014[98]
Tetrahedral DNA nanostructures (TDN)	DNA single-stranded self-assembly to form tetrahedral nanostructures	DPSC		Altered cell cycle progression and accelerated cell proliferation process; Up-regulation of osteogenic markers such as RUNX-2, ALP, OPN and OCN	The notch signaling pathway is activated to some extent to promote cellular osteogenic/odontogenic differentiation	Zhou M et al/2018[99]

Tetrahedral DNA nanostructures (TDN)	Single-stranded DNA (ssDNA) self-assembles by complementary base pairing	DPSC	Concentration of 250 nmol / L	Significantly increased levels of osteogenic marker proteins such as OPN and RUNX-2	Promoting cellular value-addition and a significant increase in the expression of Wnt/β-catenin signaling pathway proteins, which can promote cellular osteogenesis	Zhou M et al/2019[100]
Tetrahedral DNA nanostructures (TDN)		DPSC		Down-regulation of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6	Under inflammatory environment, TDN inhibits the MAPK/ERK signaling pathway to protect PDLSCs, suggesting that TDN can affect cellular processes and regulate tooth-derived MSC fate from multiple pathways	Zhou M et al/2020[101]
Calcium-siRNA nanocomplexes		PDLSC	HEPE, BSA, siRNA and calcium chloride solutions were freshly prepared in RNase-free water at a 1:1:1:1 ratio	Improvement of Ca2+ biocompatibility; BSA- Ca2+ -siRNA can be transfected in the WWP1 gene under the action of TNF-α	Promotes cell proliferation, enhances cellular osteogenesis, and prevents inflammation from damaging tissues and cells	Wang Y et al/2020[102]
Bionic bone-like protofibrils within mineralized collagen (IMC)		PDLSC		Elevated ECM secretion; Increased expression of RUNX-2, TGF-β1 and Osx	Promotes cell adhesion and growth and proliferation and regulates cellular osteogenic differentiation	Zhang C et al/2017; Liu Y et al/2011[103,104]
Mineralized Keratin (M-Keratin)		DPSC		ALP, RUNX-2, DSPP, OSX, DMP-1 Expression Enhancement	Promoting cell adhesion and proliferation demonstrated that M-keratin was able to promote the differentiation of DPSC into dentinogenic cells, and it is possible that these are related to the PI3K/Akt signaling pathway, Ca2+ signaling pathway	Chen WY et al/2020[105]
Collagen membrane enriched with a layer of graphene oxide (GO)		DPSC		Increased expression of BMP-2, RUNX-2 and SP7	Enhances cell proliferation activity, promotes osteogenic/dental differentiation, and the material has an inflammation-controlling effect	Radunovic M et al/2017[106]

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https://doi.org/10.2147/IJN.S418675
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Table 2 (Continued).

Material	Characterization	Cell Type	Concentration	Results	Conclusion	Reference
Secretion of histones		DPSC		Under different conditions, secreted histones can regulate the type of DPSC differentiation	Promotes osteogenic/neurogenic differentiation of cells	Kumar A et al/2017; Kumar A et al/ 2018[107,108]
A novel scaffold combining the amino acid sequence RAD/ PRG/KLT with SAP	The average diameter of the nanofibers was 17.9 ± 1.3 nm, consistent with the number of amino acids in the peptides	DPSC		Increased expression of VEGF, CD1, Ang-14, and vWF in DPSCs	Effective cell proliferation and vascular differentiation of cells	Xia K et al/2020[109]
Water matrix (HydM) synthetic peptide nanofiber scaffolds		PDLSC	0.25% or 0.17% gel concentration	High level expression of osteogenic genes ALP, RUNX-2, osterix, etc.	PDLSCs on the surface of HydM at higher concentrations had more active proliferative properties, and, this suggests that HydM is able to promote the proliferation and osteogenic differentiation of PDLSC and, within a certain range, positively correlates with the concentration of HydM	Nagy K等, 2018[110]
Bioactive calcium-accumulating peptide nanomaterials (CAP)		PDLSC		In the CAP setting, cells increased ALP activity and calcium deposition; The osteogenic markers RUNX-2, pSmad1/5/8, OCN, and OPN were highly expressed to varying degrees	Promotes osteogenic differentiation of cells	Jo BS et al/2017[111]
Graphene oxide		DPSC		Increased expression of BMP2 and RUNX2	Graphene oxide-coated membranes were not cytotoxic and promoted adhesion and proliferation of DPSCs, increased prostaglandin E2 (PGE2) secretion at higher concentrations, and induced faster differentiation of DPSCs into adult dentin cells/osteoblasts	Radunovic M et al/2017; Ruiz ON et al/ 2011[106,112]

Graphene oxide		DPSC	Aminosilane-functionalized cortical membranes were immersed in aqueous solutions of graphene oxide at two different concentrations (5 or 10 µg/mL)		Positive effects on the adhesion and viability of DPSCs during their differentiation may also be induced by the highly wrinkled surface associated with a small increase in stiffness obtained upon GO enrichment	Di Carlo R et al/2019[113]
Liquid phase exfoliation of graphene films		SCAP		High expression of neural differentiation markers such as Ngn2, NF-M, Nestin, MAP2, and MASH1	Induction of cellular neural differentiation	Simonovic J et al/ 2022[114]
Graphene dispersions and water-soluble single-walled carbon nanotubes		SCAP		Increased expression of neural markers	Promoting SCAP neural differentiation	Simonovic J et al/ 2018[115]
TiO_2 nanorod arrays (TNRs)	Nanorod arrays prepared on polished Ti substrates using hydrothermal and sintering methods	PDLSC		Coarser TNRs showed better hydrophilicity and protein adsorption; Increased expression of ALP, Runx2 and OPN	TNRs-modified Ti matrix effectively promotes the adhesion, proliferation and osteogenic differentiation of PDLSCs, which is mainly due to the surface morphology and biological properties of the material	Li Z et al/2017[116]
Gold nanoparticles (AuNPs)		PDLSC	45 nm AuNPs	Elevated expression of Runx2, ALP, COL1 and OPN proteins	May promote osteogenic differentiation by regulating multiple signaling pathways or autophagy activation	Zhang Y et al/2021[45]
Dense monodisperse bioactive glass nanoparticles containing zinc (Zn-BAGNPs)	Uniform size with spherical morphology	PDLSC		Up-regulation of ALP, Col1a1, Osterix, osteonectin and Runx2 gene expression levels	Promoting PDLSC osteogenic differentiation	Thanasrisuebwong P et al/2022[117]

scaffold, reduced the release of *interleukin 6 (IL-6)*, down-regulated the level of inflammation, modulated cellular oxidative stress, and promotes the expression of proteins associated with cell survival and proliferation.[124] Vahideh Raeisdasteh Hokmabad et al showed that the highly porous structure formed by embedding E-caprolactone with different nanohydroxyapatite contents into alginate structure and then freeze-drying it could effectively improve the survival and proliferation of DPSCs and upregulate *ALP* levels, elevate the expression levels of the osteogenic markers *bone gamma carboxy glutamate protein (BGLAP), bone morphogenetic protein (BMP-2)*, and *RUNX family transcription factor 2 (RUNX2)* expression levels, promote cellular osteogenesis, and show some hydroxyapatite content dependence within a specific range;[80] furthermore, the Mahdieh Alipour et al further revealed that the addition of gelatin to the complex of alginate and hydroxyapatite to form an alginate/gelatin/nano hydroxyapatite (ALg/Gel/nHA) microencapsulated structure also possessed a rougher and denser surface morphology, which implied that the pulp stem cells could better adhere to its surface and proliferate more favorably, whereas *ALP, BMP-2, osteocalcin (OCN), osteonectin (ON), RUNX-2* and *dentin salivary phosphoprotein (DSPP)* content changes also proved that this material can better promote osteogenic differentiation of odontogenic MSCs.[81] Sahar Ansari et al showed that a novel hyaluronic acid/alginate nanomaterial could promote the growth and proliferation of periodontal stem cells by encapsulating them.

In contrast, varying the content of its constituents could influence their biological properties and further affect cell proliferation. It was demonstrated by the cellular expression of β-microtubulin III and *glial fibrillary acidic protein (GFAP)* that hyaluronic acid/alginate composites were able to influence the neurogenic differentiation of odontogenic MSCs. The expression of differentiation markers was higher in PDLSCs than in GMSCs.[82] These materials offer further possibilities for the direction of alginate research.

Alginate can conform to irregularly shaped bone defects, has good biocompatibility, and is favorable for ligand attachment; however, its poor mechanical strength has driven the development of alginate-based composites. Alginate and HA composites have significant advantages in bone formation. Alginate composite hydrogels have a better drug slow-release effect, and the introduction of antimicrobial agents such as nano-silver can significantly improve the antibacterial performance; if the combination of chitin and chitosan is combined, it can affect its mechanical properties to make its application more widely. The vital inclusiveness of alginate provides more selective directions for developing composite materials.

Chitosan-Based Materials

As a derivative of chitin, chitosan has sound antibacterial and anti-inflammatory effects; it has a structure similar to that of the dentin component glycosaminoglycans and has been widely studied in nanomaterials in recent years.[125] It is worth noting that chitosan is highly hydrophobic, which adds limitations to its research in the biological field. At the same time, more and more scholars have begun to modify and process it. Kaviya Baskar et al showed that they obtained a porous bio-mineralized composite scaffold by magnetically stirring and freeze-drying nano-apatite and carboxymethyl chitosan together with a Ca/P molar ratio of 1.67, which explained the high proliferation and high cellular activity of DPSCs. In contrast, the increased expression of two osteogenic and vasculogenic genes, *DSPP* and *VEGF*, indicated that the scaffold could promote the osteogenic and vasculogenic differentiation of DPSCs under different conditions.[83] While Ishwarya Gurucharan et al used the same material to add nano-hydroxyapatite (n-HAp) and carboxymethyl cellulose (CMC) in aqueous medium, followed by freeze-drying of the product, which also enhanced the expression of *ALP, osteoblasts (OPN*), which also suggests that this chitosan material, improves the osteogenic and differentiation potential of DPSCs, and regulates the cellular life process.[84] Golnaz Navidi et al invented a chitosan scaffold containing Ca-SAPO (aluminum silicate phosphate)-34 and Fe-Ca-SAPO-34, which was fabricated by freeze-drying method, and co-culturing the scaffolds with the cells resulted in increased *ALP* activity in PDLSCs, and the osteogenic markers *BGLAP, BMP-2, RUNX-2*, and *secreted protein acidic and rich in cysteine (SPARC)* were all increased and correlated with the concentrations of Ca and Fe.[85] Wen-Ta Su et al added strontium (Sr) element to chitosan fiber scaffolds, which led to a change in the morphology of SCAPs adhering to the scaffolds and a significant increase in *ALP* activity, and the expression of osteogenic genes, such as *ON* and *OCN*, confirmed that the material could promote the osteogenic differentiation of SHEDs.[86]

Chitosan and its derivatives can lower cholesterol and blood lipids and have sound immunomodulatory effects and anti-tumor activity. They are better wound healing materials as they promote healing and hemostasis and prevent tissue adhesion in wounds. The new chitosan nanomaterials have developed their advantages. They can be further regulated by extensive chemical modifications (deacetylation, complexation, acylation) to control the differentiation of stem cells, promote cell proliferation, and change their physical properties, such as water absorption and mechanical properties through inter-group interactions, which is conducive to their development in wound healing.

Bioceramics Class (Glass-Ceramic Class, Hydroxyapatite)

As an inorganic biocompatible material, bioceramics have the characteristics of being chemically stable and non-corrosive. They thus can be used for endodontic treatment in dentistry in direct contact with living tissues.[126] Many reports have investigated the biotoxicity and biocompatibility of bioceramic materials on tooth-derived mesenchymal stem cells,[127] with differentiation towards osteoblasts and fibroblasts, ie, pulp cells, being the most extensively studied.

Nano-Hydroxyapatite

Hydroxyapatite (Hap), similar to human bone tissue's inorganic components, has been commonly recognized for its excellent osteoconductive and integrative properties. However, Hap also suffers from low fracture resistance, low resorption rate, fatigue failure, and brittleness.[128] The now commonly used nano-hydroxyapatite (n-HAp) improves on this. N-HAp has a higher surface area and exhibits enhanced resorbability, higher bioactivity, and cell adhesion, in addition to its superior properties of improving stem cell proliferation and differentiation into osteoblasts leading to bone formation.[87,129] In pursuing more demanding biomaterials, many researchers have combined them with various natural/synthetic materials to form composites to solve some potential problems of pure n-Hap biomaterials.[130]

Nanohydroxyapatite particle size is close to apatite crystals naturally occurring in human bone tissue, which has better biocompatibility and is commonly used to guide tissue regeneration and bone regeneration. Ahmed Khaled Hanafy et al simultaneously evaluated the promotional effects of mineral trioxide aggregates (MTA) and n-HAp on the odontogenic differentiation of DPSCs by examining the gene expression of *ALP, OPN, RUNX family transcription factor 1 (RUNX1), OCN*, and collagen genes. They found that both groups of genes were expressed. However, nanohydroxyapatite odontogenic genes were more highly expressed than MTA. In contrast, n-Hap's increased potential for odontogenic differentiation may be due to its chemical composition and surface morphology.[87]

Biodegradable natural polymers synthesize composite structures with good mechanical properties and biocompatibility, while HAp can support alginate and enhance the osteoconductivity of composite scaffolds. Turco G et al successfully developed alginate/hydroxyapatite (Alg/HAp) composite scaffolds.[131] Sancilio S et al evaluated the cytotoxic response of DPSCs to Alg/HAp scaffolds with lactate dehydrogenase (LDH) assay, moreover verified the potential of mineralization and differentiation based on DPSCs on Alg/HAp composite scaffolds, and not only evaluated the biocompatibility of the new constructs but also found that through the experiments related to the osteogenic differentiation of DPSCs and the deposition of mineralized matrix, their physiological functions are closely related to redox homeostasis. This homeostasis is regulated by activating the enzymatic antioxidant catalase.[88] On this basis, they further found that in the Alg/Hap scaffold/DPSCs model, the degree of inflammation was increased within seven days, but after seven days, inflammation and cytokine production were significantly reduced, but to varying degrees, which may be attributed to the fact that the cells avoided inflammation by increasing the level of phosphorylated *extracellular regulated protein kinases (Erk) 1/2*, in addition, Alg/Hap biocomposites increased the DPSCs survival and proliferation-associated protein expression and was shown to favor the intracellular balance that exists between oxidative stress response and DPSCs differentiation by changes in the molecular axis *NF-E2-related factor 2 (Nrf2)/ PGE2 / IL-6*.

In recent years, the research on nanoscale hydroxyapatite materials has made significant progress, and researchers have mainly improved the synthesis method, perfected the molecular design, and utilized the principle of bionics to regulate the composite materials to match the bone growth rate. Previous investigations have shown the role of nano Hap materials in stimulating stem cell osteogenesis and triggering angiogenesis and osteogenesis through immunomodulatory mechanisms, respectively. Hap's excellent osseointegration ability and bioactivity have led to a wide range of directions for its development, which can be applied in different biomedical fields.

Bioactive Glass-Like Materials

Bioactive glass is a bioactive material capable of bonding to bone; it has been shown to stimulate cell proliferation and influence new bone formation through the release of ions and surface apatite crystals; it is essentially a product of a network-like polymerization of silicates and phosphates; with different modifying compositions, to obtain other mechanics of machinery and biological properties.[132] Reza MooMoonesi Rad Rnesi Rad et al received a new bioactive glass by performing boron modification; they found that this new material, with larger particle size, contains a calcium Ca/P ratio closer to that of hydroxyapatite, and increasing the boron content brings this ratio closer to hydroxycarbonate apatite. This finding explains the excellent degree of adhesion and growth of DPSCs on it. In addition, boron-containing bioactive glasses have been shown to promote osteogenic differentiation of DPSCs by upregulating ATPase activity and the degree of calcium deposition.[89] Ahmed El-Fiqi et al, on the other hand, fabricated amine-functionalized Cu-doped bioactive glass nanospheres by doping Cu. Under the co-culture of DPSCs at 37°C, the osteogenic/dentogenic genes *collagen type I (COL-1), dentin matrix protein 1 (DMP-1), DSPP*, and *OCN* of the cells were significantly upregulated, which proved that such nanospheres could promote DPSCs' osteogenic-dentinogenic differentiation, which they interpreted as a role of silicate and calcium ions.[90] Jae Hwa Ahn's study found that a mesoporous bioactive glass nanoparticle (MBN)/GO composite was fabricated by the sol-gel method combined with graphene oxide (GO) after modification of bioactive glass. After autoclaving, this powder was made into a coating and co-cultured with cells at 37°C. This material absorbed the advantages of both and was able to promote the proliferation of DPSCs better and increase the expression of ALP activity, as well as osteoblastic genes, such as *DSPP, DMP-1, RUNX-2, BMP-2*, and *matrix extracellular phosphoglycoprotEin (MEPE)*, which suggests that this novel material can regulate the life course of DPSCs and improve the differentiation potential.[91] Yeonju Choi A novel mesoporous nanoparticle was fabricated by adding Zn, a protein hydrolase inhibitor capable of degrading ECM, to bioactive glass, which was sterilized and placed in tubes with DMEM for co-culturing with cells. It had a significant effect on enhancing both cellular activity and *ALP* activity.[133] Maryam Khoroushi et al fabricated polyhydroxy butyrate (PHB)/chitosan/nano-bio-glass (nBG) nanofibrous scaffolds that were able to improve the adhesion and cell viability of SHEDs and were effective in increasing the expression of *DSPP* and *ALP* to promote tooth-forming differentiation.[92]

Synthetic Class Materials (Polycaprolactone)

Synthetic-based materials are a class of materials that polymerize small organic molecules into macromolecular substances through chemical synthesis, which makes these materials promising in terms of regenerative medicine fields, such as tissue engineering, drug delivery, and in vivo implants, since they seldom induce immune responses in vivo, as well as their excellent biocompatibility and biological properties.[134]

Polycaprolactone

Poly(ε-caprolactone) (PCL), a synthetic aliphatic polyester and a biocompatible absorbable material, is commonly used in biomedical fields. However, its application has some limitations due to the weak adhesion of cells on its surface.[135,136] To overcome its shortcomings, PCL nano synthesis materials, which are biodegradable, non-toxic, and stable, are often used in practical applications and have been shown to have different degrees of positive effects on the proliferation, viability, adhesion, and differentiation of various cells.[137–139] In the context of these studies, the application of PCL nanomaterials in repairing oral and maxillofacial tissue defects is also expected.

Hosseini FS et al prepared PCL-poly(ethylene oxide) (PEO) blends filled with β-glycerophosphate (β-GP) by electrostatic spinning method and showed that the scaffolds did not have any cytotoxicity. B-gp could be released for an extended period after the cultivation of DPSCs. The scaffolds promoted osteogenic differentiation of DPSCs by causing *RUNX-2, COL-1, ON*, and *osteocalcin (OSC)* Upregulation of *RUNX-2, COL-1, ON*, and *OSC* gene expression promotes osteogenic differentiation of DPSCs, in which β-GP plays a significant role.[93] Furthermore, Ma L et al prepared berberine/polycaprolactone/collagen (BBR/PCL/COL) scaffolds by applying emerging PCL synthetic materials by electrostatic spinning. They used the scaffolds with 50 and 75 μg/mL BBR, which had better biocompatibility and pro-differentiation ability, to conduct an in-depth study of DPSCs. The results showed that the scaffolds promoted DPSCs' osteogenic differentiation through the up-regulation of osteogenesis-related genes *ALP BMP-2, OCN*, and *COL-1* expression contributing to bone differentiation, facilitating the acceleration of maxillofacial bone defect repair.[94] To enhance cellular responses using biodegradable scaffolds and stimulating factors, Alipour M et al also evaluated the effect of zeolite on DPSCs cultured on poly(e-caprolactone)-poly(ethylene glycol)-poly(e-caprolactone) (PCL-PEG-PCL) nanofibers, and the results showed that its highly porous structure favored the growth and proliferation of DPSCs, and the expression of *OCN, BMP-2, RUNX −2* and *DSPP*, and the up-regulation of the expression of critical genes suggesting the promotion of the osteogenic differentiation potential of DPSCs. However, there was no significant change in the presentation of the odontogenic differentiation gene *DSPP*, indicating that the scaffolds had almost no effect on the odontogenic differentiation of DPSCs.[95]

Although composites can affect cell survival by releasing relevant biological factors, it has been found that adding nHA to PCL improves the physicochemical properties and biological effects of the scaffolds.[140] Azaryan E et al further compared the effects of PCL/nHA and PCL/*Elaeagnus angustifolia* extract (nHAEA) on DPSCs. The latter was found to not only promote the activity and proliferation of DPSCs by improving their adhesion to scaffolds but also increase the expression of marker genes for odontogenic differentiation (*BMP2, RUNX2*, and *DSPP*) to enhance osteogenic/dental differentiation of DPSCs.[96] In addition to this, a novel polyvinyl alcohol (PVA)-polycaprolactone (PCL) bioceramic (HAB) electrostatically spun composite scaffold has also attracted the attention of researchers due to its ability to overcome the defects of PCL's hydrophobicity. Prabha RD et al observed the uniform distribution, survival, and proliferation of DPSCs on scaffolds, which were tested to enhance DPSCs' ability to differentiate from other scaffolds by increasing *ALP* activity, osteoblast gene expression, and the ability to form a mineralized matrix to promote osteogenic differentiation of DPSCs, providing an ideal material for maxillofacial bone tissue engineering.[97] Wang W et al fabricated an injectable nanofibrous microsphere (NF-MS), which, with the addition of the osteogenic factor *BMP-2*, was effective in increasing the expression of the osteogenic and odontogenic markers of SCAPs, *Col-1, bone sialoprotein (BSP), OCN*, and *DSPP*, suggesting that NF-MS can promote the osteogenic differentiation of SCAPs.[141] Wen-Ta Su et al added strontium phosphate to polycaprolactone to form a novel nanofiber material that increased *ALP* activity and promoted the expression of osteogenic genes in SHEDs.[98]

The advantages of PCL are its adequate cell adhesion and proliferation, good mechanical strength, and slow degradation rate, and the biodegradation of PCL-based scaffolds is driven by a hydrolysis reaction without the need for enzymes or catalysts.[142] Several studies have shown that PCL nanocomposites may improve the adsorption of osteogenic factors on their surfaces, thereby improving the mineralization process of bone tissue regeneration. Compared with PCL, composite nanomaterials can enhance cell spreading and adhesion, have more powerful healing efficacy, and have great potential for oral soft and hard tissue repair.

Bio-Organic Materials (Nucleic Acid-Based Materials, Protein-Peptide-Based Materials)

Bioorganic materials, represented by nucleic acids and protein peptides, have unique biological properties, interact with living organisms, precisely control their bodily functions by their complex three-dimensional structures,[143] and have unique advantages in biodegradation and recyclability.

Nucleic Acid-Based Materials

Tetrahedral DNA nanostructures (TDN) are composed of four single-stranded DNA (ssDNA) molecules, and unlike pristine DNA, TDN is permeable, biocompatible, and biodegradable to cellular membranes, and it can enter the cell and direct gene expression through caveolin-mediated endocytosis.[144,145] The research on TDN for cells has become a hot topic nowadays. It has been demonstrated that TDN is inextricably linked to several signaling pathways, including *Wnt/β-catenin, Akt/Nrf2/HO-1, PI3K/AKT/mTOR*, which implies that TDN can regulate cell proliferation, migration, apoptosis, oxidative stress, anti-inflammatory, anti-inflammatory, anti-infective and immunomodulatory activities.[146–149] Mi Zhou et al indicated that after adding TDN to conventional DMEM to reach a concentration of 250 nmol/L, dental pulp stem cells exposed to TDN had altered cell cycle progression and accelerated cell proliferation process; in addition, TDN upregulated the content of osteogenic markers, such as *RUNX-2, ALP, OPN, OCN*, and promoted the process of cellular osteogenesis. Meanwhile, the notch signaling pathway was also somewhat activated, promoting osteogenic/odontogenic differentiation of DPSCs.[99] Meanwhile, Mi Zhou et al also explored the effect of TDN on PDLSCs. They found that after exposing PDLSCs to 250 nmol/L TDNs solution, the content of osteogenic marker proteins, such as *OPN* and *RUNX-2*, was significantly increased. The expression of *Wnt/β-catenin* signaling pathway proteins was elevated considerably, explaining the TDN mechanism promoting osteogenesis. Interestingly, under the inflammatory environment, TDN could also protect PDLSCs by down-regulating pro-inflammatory factors, such as *tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β)*, and *IL-6*, and inhibiting the *mitogen-activated protein kinase (MAPK)/ extracellular regulated protein (ERK)* signaling pathway, which indicated that TDN could affect cellular processes and handle the fate of tooth-derived MSCs from multiple tracks.[100,101] In addition, Yang Wang et al formed a stable nanoscale complex, BSA-CAa2+-siRNA nanocomposite (5 μM siRNA, 125 μg/mL BSA, and 250 mM CaCl2), by chelating bovine serum albumin (BSA) and calcium ions (Ca2+) and then combining them with small interfering RNAs (siRNAs), which were added to α - MEM at a 1:50 fresh dilution and the cells were incubated for an additional 3.5 hours. This improved the biocompatibility of Ca2+ and promoted the proliferation of PDLSCs. At the same time, BSA- Ca2+ -siRNA could be transfected with the *WW domain-containing E3 ubiquitin-protein ligase (WWP1)* gene under the action of the inflammatory factor *TNF-α* to enhance the osteogenesis of PDLSCs and to prevent the destruction of tissues and cells by inflammation.[102]

Currently, the research of nucleic acid-based nanomaterials is more popular with TDN, whose unique three-dimensional structure responds to stimuli from the surrounding environment and thus regulates biological behaviors such as cell differentiation, anti-inflammatory response, and value-added migration and can be used for molecular and targeted drug delivery.TDN, a new type of nanomaterial that can significantly affect cell behavior, has great potential in bone tissue engineering based on PDLSCs.

Protein and Peptide Materials

Collagen is an essential ECM component and the most abundant protein in bone. Recently, a newly synthesized collagen apatite that can mimic natural bone components has become a hot research topic due to its excellent mechanical properties, strength, and biocompatibility.[150–152] Ci Zhang et al fabricated a bionic bone-like protofibrillar internal mineralized collagen (IMC) with type I collagen as a scaffold and nano-apatite fibers deposited therein. Their study showed that by sterilizing the scaffold and invading it into PBS, and then inoculating it with porcine PDLSCs, the cells on the surface of this scaffold could better secrete ECM and express more *RUNX-2, transforming growth factor-β1 (TGF-β1)*, and *osterix (OSX)*, which were not occurring on the scaffolds of hydroxylated apatite alone. Apatite scaffolds did not happen, implying that IMC scaffolds can promote adhesion and growth proliferation of PDLSCs and regulate osteogenic differentiation of PDLSCs.[103,104]

Keratin is an intermediate filament that can be formed in various epithelial cells, and it has recently been shown that keratin can regulate multiple processes of cell fate.[153,154] Wu-Ya Chen The synthesized mineralized keratins (M-keratins) further increased the particle size of keratins into nanoparticles separated from each other compared to normal keratins and blank control groups, which, together with the effect on calcium and phosphorus ion concentration, explained their promotion of adhesion and proliferation of DPSCs. In contrast, the increased expression levels of *ALP, RUNX-2, DSPP, OSX*, and *DMP-1* proved that M-keratin could promote the differentiation of DPSCs into dentinogenic cells, and these could be related to the *PI3K/Akt* signaling pathway and Ca2+ signaling pathway.[105] Lan Ma et al formed a novel nano scaffold by combining berberine (BBR), polycaprolactone, and collagen, which had good biocompatibility and the best induction of the osteogenic genes *ALP, BMP-2, OCN*, and *COL-1* when BBR was at a moderate concentration, which resulted in an effective enhancement of the osteogenic differentiation potential of DPSCs.[94] Milena Radunovic showed that enriching a layer of GO on collagen membrane could effectively increase the proliferative activity of DPSCs, and could increase the expression of *BMP-2, RUNX-2*, and transcription factor SP7, which indicated that this material could promote the osteogenesis of DPSCs. It is worth noting that after increasing the concentration of GO, the expression of *TNF-α* and *COX-2* genes was down-regulated accordingly, which indicated that this material has a role in controlling inflammation.[106]

Also, Ajay Kumar's multiple studies showed that secreted histones upregulated the levels of *nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF)*, and *neurotrophin 3 (NT-3)* in DPSCs, suggesting a regulated and accelerated process of neural differentiation, they also demonstrated that in the presence of osteogenic inducing factors, the DPSCs' osteogenic markers *DSPP, ALP, and RUNX-2, OCN* were highly expressed. Thus, it indicates that secreted histones can regulate the type of differentiation of DPSCs under different conditions, providing clues for further studies.[107,108] Self-assembled peptide (SAP) is a nanomolecular material synthesized by automated solid-phase synthesis. Different amino acid sequences can obtain various biological activities.[155]

Kun Xia et al fabricated a novel nano scaffold by combining the amino acid sequence RAD/PAG/KLT with SAP, which effectively promoted the proliferation of DPSCs and could significantly increase the expression of *VEGF, CD1*, and *von Willebrand factor (vWF)* in DPSCs, and the high level of these vasculogenic genes provided strong evidence for the material's ability to promote vasculogenic differentiation of DPSCs provides strong evidence.[109] Krisztina Nagy et al investigated the effect of aqueous matrix (HydM) synthetic peptide nanofiber scaffolds on PDLSCs. They found that PDLSCs on the surface of HydM at higher concentrations had more active proliferation characteristics and high levels of expression of osteogenic genes, such as *ALP, RUNX-2*, and *OSX*, which suggests that HydM can promote the proliferation and osteogenic differentiation of PDLSCs and that it is positively correlated with the concentration within a specific range, a positive correlation with concentration was observed.[110] Beom Soo Jo et al developed a bioactive calcium-accumulating peptide nanomaterial (CAP) by chemically coupling a functional partially synthesized peptide to a hydrogel. Their study showed that PDLSCs increased ALP activity and calcium deposition in the CAP environment. The osteogenic markers *RUNX-2, pSmad1/5/8, OCN*, and *OPN* were expressed to varying degrees, suggesting that the CAP can promote the osteogenic differentiation of PDLSCs.[111]

The essence of bio-nanotechnology lies in applying nanotechnology/nanomaterials to solve biological problems, eg, protein nanotubes can fulfill various functions in drug delivery, biosensors, and energy storage, and their different structures have different applications in multiple fields. Protein and peptide nanocomposites have better biocompatibility and bioavailability than other materials and can promote osteogenic and odontogenic differentiation of cells and control inflammatory responses to facilitate repair. Unique peptide materials such as antimicrobial peptide nanocomposites have shown remarkable efficacy in tissue engineering biomedical applications as they are antibacterial, anti-biofilm, and promote wound healing.[156]

Bioinorganic Materials (Graphene-Like Materials, Metal Nanomaterials)

Bioinorganic materials include bioinorganic nonmetallic materials and metallic materials, the former represented by nanocarbon, which has been widely used in biosensing, drug carriers, and disease diagnosis;[157] the latter is commonly used in tissue replacement, such as titanium for orthopedic implants. Such materials have great potential in the clinic.[158]

Graphene-Based Family

Graphene is a single atomic layer form of carbon, and its family has various derivatives, GO, reduced graphene oxide (RGO), and graphene nanosheets, which are widely used in biomedical engineering due to their excellent biological properties.[159,160] In recent years, more and more researchers have been integrating graphene and its derivatives with drugs, antibodies, and other biomolecules and designing nanocomposite carriers utilizing their good ductility, elasticity, and biocompatibility.[161] The role of graphene in the specific differentiation of human mesenchymal stem cells has been reported, and graphene and its derivative nanocomposites can also promote the osteogenic and proliferative potential of stem cells due to their physicochemical and biological properties.[162,163]

Based on the study of graphene-based nanomaterials to promote osteogenic differentiation of bone marrow mesenchymal stem cells,[162,164] more reports based on tooth-derived mesenchymal stem cells appeared in the public eye. Graphene has been reported to be able to aggregate osteogenic differentiation precursors through non-covalent π-bonds, thus promoting osteogenic differentiation of MSCs.Zhang L et al chose to investigate how graphene affects the proliferation and differentiation of DPSCs using the poly(4-vinyl pyridine) (P4VP) system. They found that graphene additions were extensively mineralized on the planar surfaces. In contrast, on the microfibrous surfaces, mineralization was significantly reduced due to the suppression of the expression of *OCN* genes, which could be because graphene on flat scaffolds can be in direct contact with DPSCs. Its π-bonding allows growth factors released by DPSCs to be better absorbed by the surface, thus accelerating biomineralization on the scaffolds.[165]

Graphene oxide is a highly oxidized form of graphene. Still, in contrast to graphene's low solubility, GO is highly soluble in water and easily binds to other biomolecules due to the presence of functional groups such as carbonyl, carboxyl, and epoxy groups because of its surface functionalization. GO has lower cytotoxicity than graphene and other derivatives, which are properties that confer great potential in biomedical fields.[106,166] Radunovic M et al showed that graphene oxide-coated membranes were not cytotoxic and promoted the adhesion and proliferation of DPSCs, increased *PGE2* secretion at higher concentrations, and induced a faster differentiation of DPSCs into dentinogenic/osteoblastic cells, as compared to conventional guided tissue regeneration (GBR) membranes.[106,112] A study by Di Carlo et al found that positive effects on the adhesion and viability of DPSCs during their differentiation may also be induced by a highly folded surface associated with a slight increase in stiffness obtained during GO enrichment.[113] The research and application of composites are also increasing year by year. Ahn JH et al synthesized mesoporous bioactive glass nanoparticles (MBN)/GO composites using the sol-gel method and colloidal treatment and found that the expression of *DSPP* and *RUNX-2* were both significantly upregulated when DPSCs were cultured and concluded that MBN/GO composites promote, through the *Wnt/β-linker protein* signaling pathway, the odontogenic differentiation and induced dentin formation.[91] Liu J et al fabricated a novel multi-walled carbon nanotube material that significantly upregulated *hypoxia-inducible factor-1 (HIF-1α)*, and *VEGF* expression, which promoted vasculogenic differentiation of SCAPs.[49,76] Liquid-phase exfoliation of graphene films prepared by Simonovic J et al for SCAPs with neurogenic induction, the high expression of neural differentiation markers such as *neurogenin-2 (Ngn2), neurofilament triplet M (NF-M), Nestin, microtubule-associated protein-2 (MAP2*), and *mammalian achaete-scute homolog-1 (MASH1)* demonstrated that this type of material could induce neural differentiation of SCAPs;[114] they also investigated the effect of graphene dispersion and water-soluble single-walled carbon nanotubes on the SCAPs neural differentiation, and like the above neuro markers, such materials can also promote SCAPs neural differentiation.[115]

Research on carbon nanomaterials has been emphasized in various fields. Standard methods to improve functionality include improved hydrophilicity, biocompatibility, and functionalization for cellular uptake and selectivity.[167] Graphene nanomaterials, as one of the popular materials, can influence the adhesion, proliferation, and differentiation of dental-derived stem cells to promote bone regeneration and wound healing. This material has some antimicrobial activity and can interact with immune system cells to increase biocompatibility and decrease the amount of apoptosis. Existing dental materials show improved properties with the addition of graphene.[168] In conclusion, graphene-based nanomaterials have emerged as promising scaffolds for various biomedical applications.

Metallic Nanomaterials

Metal nanomaterials at the nanoscale have properties such as melting point and ductility that are far different from the macroscopic scale, and they can also have different effects on cells when they come into contact with each other.[169] Metal nanomaterials such as Ti, Mg, Zn, and alloys have a broad scope of development in biomedicine under their high strength, good biodegradability, antimicrobial activity, and stem cell-inducing properties. Their stem cell-induced properties have a better application prospect in the repair of oral and maxillofacial tissue defects. Degradable metal nanomaterials also mean that the implants can be metabolized and absorbed by human tissues or cells, reducing the risk of sequelae in the human body.[170]

Titanium (Ti) and its alloys have good biocompatibility, mechanical properties, and corrosion resistance.[39] However, their excellent corrosion resistance makes them often exhibit the defects of slow biological response, low osseointegration, and lack of antimicrobial properties, and nanoscale surface modification is an effective means to facilitate the solution of the above problems and to confer functionality to implants (eg, enhancement of osteoconductivity).[170] Nanomorphs are challenging to form on dentin sections, but various nanomorphs are easily prepared on Ti. Based on the observation of the effects of titanium and its derivative nano morphisms on the function of periodontal membrane stem cells (PDLSCs) and periodontal regeneration, Gao H et al found that titanium dioxide nanotubes (NTs) enhanced the initial adhesion, diffusion, and collagen secretion of PDLSCs, and that there was a size effect, ie, NT5 and NT10 tended to be more potent than NT20. In contrast, ectopic implantation of a Ti/cell slice/HA complex model was able to regenerate periodontal tissue and produce dense collagen fiber bundles. Regarding modifying Ti for better performance, Li Z et al observed that rutile TiO2 nanorod arrays (TNRs) have good physicochemical and differentiation-promoting properties, TNRs modified Ti. The obtained TNRs-modified Ti matrix effectively promoted the adhesion, proliferation, and osteogenic differentiation of PDLSCs, and the differentiation-promoting properties could be attributed to two reasons: ① Mechanical factors: the TNRs good roughness and wettability of the surface ② Biological factors promote osteogenic differentiation of PDLSCs by inducing cytoskeletal F-actin reorganization and cell shape change.[116]

AgNPs are powerful disinfectant antimicrobial agents widely used in the environmental and medical fields. Dentistry commonly uses them to fight patient infections and osseointegration.[171] AuNPs have the characteristics of simple synthesis, easy surface modification, and unique physicochemical properties. Therefore, they have aroused great interest in biomedicine. Although there have been some reports on the toxicity of AuNPs, this mainly depends on the shape, size, and surface chemistry at the time of preparation. It has been reported that AuNPs can promote the osteogenic differentiation of MSCs.[172–174] Zhang Y et al treated PDLSCs with 45 nm AuNPs based on a previous study and found that they exhibited better osteogenic differentiation and ECM mineralization, which may be due to the fact that: i) mechanical nanoparticle stimulation of nanoparticles induces biochemical changes and regulates *p38 / MAPK, ERK / MAPK or Wnt/β-catenin* signaling pathways to promote osteogenic differentiation ② AuNPs may affect cytoskeletal structure through endocytosis, which then promotes osteogenic differentiation through autophagy activation.[45] In addition to pure metal nanomaterials, metal composite carriers have also received extensive attention, Thanasrisuebwong P et al have developed dense monodisperse bioactive glass nanoparticles (Zn-BAGNPs) containing zinc, and they found that Zn-BAGNPs bring toxic effects to tooth-derived MSCs to a certain extent, which is perhaps since Ca, Sr, and Zn incorporation altered the silica network structure and accelerated its degradation. Zn-BAGNPs also promoted the osteogenic differentiation of PDLSCs by upregulating the expression levels of *ALP, COL1A1, OSX, ON*, and *RUNX2* genes.[117]

There is a wide variety of nano-metallic materials, each showing different properties and efficacy. Silver nanoparticles are known for their antimicrobial properties, gold nanoparticles for their anti-inflammatory effects, and copper nanoparticles for their antimicrobial effects. Studies have shown that various nano-metallic materials have shown better stem cell induction and can inhibit biofilm formation, which has a more significant potential for application in the dental field.

Tooth-Derived Stem Cell and Material Regeneration Strategies for Various Types of Tissues

Based on the complex three-dimensional anatomical structure and the bacterial environment connected with the outside world, oral and maxillofacial tissue repair always needs to rely on the joint action of multiple tissues and cells and the regeneration of bone, blood vessels, nerves, and odontogenic stem cells in pulp tissue induced by nanomaterials provides a more comprehensive restoration option in the clinic.

Please refer to Table 3.

Table 3 Study on DMSCs in Tissue Differentiation

Type of Tissue Differentiation	Examples	Reference
Bone tissue differentiation	DPSCs cultured on nHAC/PLA express favorable cellular osteogenic and lipogenic STRO-1 and vimentin	Liu HC et al/2011[175]
Bone tissue differentiation	PCL scaffolds containing simvastatin (SIM) were cultured with PDLSCs, and PCL-SIM scaffolds were found to increase osteogenesis by upregulating the expression of type I collagen and ALP	Zhao B et al/2020[176]
Bone tissue differentiation	Adult gingival-derived mesenchymal stem cells (hGMSC) were cultured on electrostatically spun polycaprolactone (PCL) scaffolds, and ALP and alizarin red results supported their osteogenic differentiation potential	Jauregui C et al/2018[177]
Bone tissue differentiation	Titanium dioxide nanomaterials increase the expression of interleukin-13 α 2 receptor and the secretion of transforming growth factor β 1, which stimulate each other to promote gingival epithelial cell osteogenic differentiation	Ishikawa T et al/2021[178]
Vascular tissue differentiation	GMSCs have a stronger ability to contribute to fibroblast proliferation and pro-angiogenesis on alginate-gelatin methacrylate (GelMA) hydrogels compared to BMSCs	Ansari S et al/2021[179]

(*Continued*)

Table 3 (Continued).

Type of Tissue Differentiation	Examples	Reference
Vascular tissue differentiation	Bioactive calcium phosphate cement (CPC, α-tricalcium phosphate-based) material from zinc bioglass (ZnBG) promotes angiogenesis and odontogenic differentiation of DPSCs	Zhang J et al/2015[180]
Vascular tissue differentiation	An in situ tissue-engineered scaffold (iTE scaffold) increases microvessel diameter and density and enhances angiogenesis in PDLSCs	Ding T et al/2021[181]
Vascular tissue differentiation	Nanofiber sponge-like microspheres (NF-SMS) can significantly promote vascular endothelial growth factor (VEGF) expression in DPSC and induce angiogenesis under hypoxic conditions NF-SMS can activate HIF-1α	Kuang R et al/2016[26]
Neural tissue differentiation	Positive effects of novel scaffolds made of alginate and hyaluronic acid in promoting neural tissue regeneration from odontogenic stem cells	Luo L et al/2020[182]
Neural tissue differentiation	Scaffolds formed by chitosan and essential fibroblast growth factor regulate the differentiation of DPSCs	Zheng K et al/2021[183]
Dental pulp tissue differentiation	Biologically active glass (BG) enhances the proliferation and migration of DPSC and promotes the differentiation of DPSC into dentinogenic cells	Wang S et al/2014[184]
Dental pulp tissue differentiation	Formation of novel nano complexes by adding strontium (Sr) to BG enhances the expression of osteogenic and odontogenic genes, resulting in a significant enhancement of the odontogenic effect of DPSCs	Huang M et al/2016[185]
Dental pulp tissue differentiation	PLGA/gelatin electrostatically spun sheets (APES) co-cultured with DPSCs promote DPSCs to complete odontogenic differentiation	Chen G et al/2015[186]

Bone Tissue Differentiation

Bone regeneration is one of the most important means of restoring facial aesthetics and regaining oral function, which often requires regenerative materials with excellent biocompatibility and osteoblast inducibility. Based on the primitive osteogenic ability of cells such as PDLSCs and DPSCs, nanomaterials such as collagen-based nanohybrids (nHAC), PLA, and graphene have a solid potential to enhance osteogenic differentiation. Liu HC et al found that DPSCs cultured on nHAC/PLA expressed STRO-1 and vimentin, which are favorable for cellular osteogenesis and lipogenesis, and that the additional addition of recombinant human bone morphogenetic protein 2 (rhBMP-2), it was more able to increase autologous bone formation by rising gene expression.[175] As a widely used scaffold material, PCL also has a more significant effect on PDLSCs; Zhao B et al cultured PDLSCs on PCL scaffolds containing simvastatin (SIM) and found that PCL-SIM scaffolds increased osteogenesis by upregulating the expression of *COL-1* and *ALP*.[176] Jauregui C et al decided to spin PCL scaffolds in the cultured adult GMSCs electrostatically, and the *ALP* and alizarin red results supported their osteogenic differentiation potential.[177]

In addition, Ishikawa T et al probed the osteogenic differentiation potential of gingival epithelial cells with titanium dioxide nanomaterials. They showed that this resulted in a rise in the expression of interleukin-13 α 2 receptor and an increase in the secretion of *TGF-β1*. The two stimulated each other, promoting gingival epithelial cell osteogenic differentiation.[178]

Vascular Tissue Differentiation

Vascular regeneration has a more critical position in soft tissue reconstruction; a rich blood supply provides nutrition to promote repair and helps prevent all kinds of complications due to nutritional disorders. Many biomaterials have been widely studied in the field of vasculogenesis. Ansari S et al developed an alginate-gelatin methacrylate (GelMA) hydrogel, which, compared to BMSCs, gingival mesenchymal stem cells (GMSCs) promoting *TGF-β1, primary fibroblast growth factor (bFGF)*, and *VEGF*, with a more vital ability to contribute to fibroblast proliferation and pro-angiogenesis.[179] Zhang J et al, on the other hand, developed a bioactive calcium phosphate cement (CPC, α-tricalcium phosphate-based) material incorporating zinc bioglass (ZnBG), and the results showed that the material, through the up-regulation of integrins and activating signaling pathways such as *Wnt, MAPK*, and *NF-κB*, thereby promoting angiogenesis and odontogenic differentiation of DPSCs.[180] Ding T et al prepared core-shelled fiber scaffolds releasing *bFGF* and *BMP-2* enhanced angiogenesis of PDLSCs, macrophage polarization, and enhanced osteogenic differentiation of PDLSCs through immune mechanisms.[181] Furthermore, Kuang R et al assembled nanofiber spongy microspheres (NF-SMS). They found that under hypoxic conditions, NF-SMS activated *HIF-1α*, significantly promoted *VEGF* expression in DPSCs, and induced angiogenesis, possibly due to cell-cell interactions.[27]

Neural Tissue Differentiation

As a popular nanomaterial for influencing the neural differentiation of stem cells, hydrogel-like materials have been shown to affect the processes of growth, proliferation, and differentiation of a wide range of cells, including spinal cord neural stem cells,[187] macrophages,[188] and human neuroblastoma cells.[189] While Luo L et al showed that a novel material consisting of hydrogel, recombinant human essential fibroblast growth factor, and DPSCs filled with cellulose was able to effectively promote the proliferation of DPSCs, and the anti-human neural-specific markers of *GFAP, β-microtubulin III, S-100*, and *MBP* were all highly expressed;[182] Ansari S et al simultaneously applied alginate and hyaluronic acid at the same time to make a novel scaffold, which also had an effect on the proliferative activity of PDLSCs, and the expression of *β-microtubulin II*I and *GFAP* was increased under the impact of continuously released *β-nerve growth factor (β-NGF)*, confirming the positive effect of hydrogel in promoting the regeneration of neural tissues of odontogenic stem cells;[179] in addition to the above materials, Zheng K et al have also explored the effect of scaffolds formed by chitosan and primary *FGF* on DPSCs; in their study, cell viability was unaffected, and the expression levels of the neural differentiation markers, *GFAP, central neural specific Protein (S1-00β)*, and *β-microtubulin III* were significantly increased, demonstrating that this material can also regulate the differentiation process of DPSCs.[183]

Pulp Tissue Differentiation

Regeneration and repair of dental pulp have always been a challenge for treating endodontic diseases, and the excellent prospects of stem cells and nano-bioactive materials bring new hope for this challenge. Wang S et al explored the effect of bioactive glass (BG) on DPSCs, and they found that under the influence of BG, the proliferation and migration ability of DPSCs was enhanced, and the newborn dentin was visible, which indicated that BG promoted the differentiation of DPSCs into dentin-forming cells;[184] in addition, Huang M et al added Sr to BG to form a novel nano-complex, which was able to enhance the expression of osteogenic genes, such as *RUNX-2, OCN, MEPE, BMP-2*, and *ON*, as well as the face of *DSPP* and *DMP-1* dentin-forming genes, which undoubtedly indicated that, under the condition, the DPSCs The tooth-forming effect of DPSCs was significantly enhanced;[185] Xia K et al developed The Arginine - Glycine - Aspartic acid (Arg-Gly-Asp, RGD) and VEGF-assembled peptide that was able to provide 3D scaffolds for DPSCs, upregulate the levels of their osteogenic and tooth-forming genes, such as *ALP, DMP14*, and *DSPP*, and was able to significantly increase the proportion of coronal dentin in a rat molar model, which suggests that this material has a positive effect on dentin differentiation;[109] Chen G et al on the other hand, fabricated a PLGA/gelatin electrostatically spun sheet (APES), and by co-culturing it with DPSCs, demonstrated that DPSCs secreted positive ECM proteins *COL-1, collagen type III (Col-3), fibronectin (FN), and Laminin (LN*), upregulated the odontogenic markers *DMP-1, DSPP*, and *VEGF*, and markedly down-regulated from the early osteogenic markers *ALP, BSP*, and *RUNX-2*, which suggests that DPSCs are able to accomplish odontogenic differentiation in the presence of this material.[186] In the field of endodontic differentiation, nano complexes composed of BGs have become an emerging material as a direction of the investigation.

Summary and Prospects

In 1959, American physicist Richard Feynman, "the father of modern nanotechnology", put forward the concept of nanotechnology, nanotechnology, and nanomaterials began to get attention, but also in 1990, after the rapid development, in recent years, due to the complexity of tissue repair in the oral and maxillofacial tissues and susceptibility to infection, nano-bioactive materials have also been used more and more widely.[190,191] As seen previously, at the nanoscale, various biomaterials exhibit cell-inducing properties that are not visible from a macroscopic perspective. For example, n-HAp can have osteogenic/dental differentiation effects on DPSCs through pro-gene expression and modulation of oxidative stress. In contrast, graphene oxide can have different inducing effects on DPSCs due to changes in its surface morphology. And n-HAp can be used as a cell-inducing agent for DPSCs: adhesion, proliferation, and osteogenic differentiation of PDLSCs. In comparison with BMSCs, although DPSCs were stronger than BMSCs in terms of cell proliferation, growth activity, and availability, *ALP* activity and osteogenic gene expression showed that their osteogenic differentiation potential was weaker than that of BMSCs.[192] Therefore, utilizing nano-bioactive materials is indispensable if the restorative capacity of tooth-derived MSCs is to be fully demonstrated.

The adverse effects of these materials cannot be ignored to ensure the safety and efficacy of nanomaterials used in clinical applications for patients. In the comparison between dental composite nanomaterials and traditional materials, although the former has a higher modulus of elasticity, the defects of its mechanical properties cannot be ignored, which may be due to the unbalanced structure and properties of the material.[193] In the process of material-cell interaction, the toxic response caused by material-induced production of biotoxic substances or disruption of the cytoskeletal network is also an essential factor affecting the repair of the organism.[194] Among them, high levels of endogenously/exogenously generated ROS often evoke the cellular autophagy pathway, and it has been shown that *TGF-β* induces senescence in PDLSCs by increasing ROS production.[195] Based on this, Li Y et al developed a conductive alginate/gelatin (AG) scaffold doped with graphene oxide (PGO) and hydroxyapatite nanoparticles (PHA) with antioxidant properties and flow cytometry demonstrated that ROS scavenging of PGO-PHA-AG scaffolds could protect the cells from damage.[196] Several studies have found that the graphene family mostly has low cytotoxicity and is dose-dependent and time-dependent; some reported that GO has no toxic effect on cell behavior, but others found that the surface charge and lateral size of GO are responsible for cytotoxicity.[197,198] In addition to possible cellular toxicity, nanomaterials have some potential risk in inducing and influencing disease development, with some studies suggesting that engineered nanoparticles (NPs) may accelerate the progression of asthma through mechanisms such as altered oxidative stress, activation or inhibition of inflammatory vesicles, and interactions with antigen-presenting cells, and exacerbate such effects when co-exposed with other risk factors.[199] Despite these drawbacks, nano bioactive materials have a place in oral and maxillofacial prosthetics due to their unique advantages. However, as a practical matter, the high cost of nanomaterials and the long production cycle are challenges that need to be overcome in social medicine.[200] In addition, the precision and stability of the produced materials are also a significant concern for most patients.

In recent years, the application of extracellular vesicles (EVs) in stem cell-based therapeutic approaches in dentistry has also become increasingly widespread.EVs are phospholipid bilayer-encapsulated particles that can be secreted and released by almost all types of cells and are mainly classified into exosomes and microvesicles (MVs).EVs are essential information carriers and are often used as biomarkers for diagnosing, prognosis, and treating disease.[201] Sundaram et al developed ginger-derived nanovesicles (GiNVs) that have remarkable stability and can be used as therapeutic agents to ameliorate or prevent chronic periodontal disease, target Porphyromonas gingivalis, and minimize the occurrence of bone loss and inflammation.[202] Yin B et al investigated mesenchymal stem cells or platelet-rich plasma-derived EVs (MSC-Evs or PRP-Evs). They found that both could inhibit the inflammatory microenvironment and reduce chondrocyte apoptosis.[203] Nanovesicles have unique advantages over nanocomposite scaffolds.AuNPs are a commonly used nanomaterial. However, most lack in vivo tumor specificity, whereas ncRNA-enriched EVs can carry drugs or nanoparticles to improve specificity and significantly enhance their efficacy.[204] For example, for protein molecules, autologous protein cargoes of EVs can be transferred to recipient cells to induce various cellular functions.[205] While aging impacts endodontic physiological changes, Iezzi I et al found that miRNAs and exosomes derived from endodontic stem cells constitute a significant nanovesicle source that can treat age-related dental lesions.[206] In addition, exosomes have an enormous potential for application in wound healing and scar attenuation. Zhao W et al used exosomes derived from mesenchymal stem cells (MSC-Exo) to down-regulate the expression of SIRT1 and inhibit the biological behaviors of fibroblasts, thereby directly or indirectly modulating the immune response during pathologic scarring, which can be applied to skin scarring, organ fibrosis, and other related diseases.[207] However, exosome production, isolation, and utilization efficiency remain challenging. Adopting strategies to enhance exosome production and activity is urgent in the current biomedical field.

The use of living organisms to create inorganic nanoscale particles is a potential new development in biotechnology, and green nanomaterials have emerged for the rational utilization of biological resources. Studies have shown that green nanomaterials are particularly suitable for drug and DNA delivery, eg, cellulose, a readily available biomolecule, is often used as a green alternative to chemical nonviral gene delivery systems.[208]

The goal of reconstructive surgery is to restore form and function, and commonly used methods such as microvascular free flap transfers often result in severe pain, sensory nerve disorders, or concomitant scar formation. On the other hand, tissue engineering techniques based on stem cell research can promote the regeneration of hard and soft tissues and induce the reconstruction of defective areas, promising an alternative to current surgical repair techniques. Cellular scaffolds have their unique biodegradability, which can provide space for the growth of cells in the surrounding tissues and guide tissue regeneration and repair by inducing osteogenic, odontogenic, and angiogenic differentiation of cells and promoting cell proliferation.[209] Multifunctionality is a prominent advantage of nanocomposites compared to existing conventional materials, and multiple functions such as targeted ligands, drug therapy, infection prevention, and imaging markers can be concentrated in a single entity, which together participates in the diagnosis and treatment of diseases. Several studies have shown that nanomaterials can be used as intrinsic antimicrobial agents (eg, AgNPs and ZnO NPs) in the promotion of wound healing and as nanocarriers for therapeutic agents to help wound healing (eg, combining antibiotics, NO), and nanomaterial scaffolds are even more widely used by virtue of their unique physical and structural properties. Nanomaterials-based wound-healing growth factors can regulate cell growth, differentiation, and migration and play an essential role in tissue repair.[210] Nowadays, nanomaterials have a wide range of applications as potential solutions for regenerative medicine in inducing mesenchymal stem cells to promote tissue differentiation. They have also gained more attention in the field of drug delivery. Therefore, this paper categorizes and summarizes the specific regulatory functions of different nano-bioactive materials and the research mechanisms on the basis of the existing studies to provide a theoretical basis for the research and development of new nano-scaffold materials.[211,212]

As more and more nano bioactive materials are being investigated for their physicochemical properties, various types of drugs and techniques are combined for disease treatment. Currently, hard tissues of the oral and maxillofacial region are mainly repaired by resetting and bone grafting. In contrast, soft tissues depend more on the body's healing and tissue grafting, which in most cases can only partially restore the morphology and function of the defective area. The demand for aesthetics is forcing researchers to look for a new direction. The use of bioactive materials and stem cell transplantation in combination to induce tissue repair in traumatized and pathologically damaged tissues has become an essential tool for future surgical repair,[213,214] and the influence of immune response and stem cell activity has made it a hot topic to consider the coexistence of bioactive materials and stem cells. In the future, with the development of modern nanoengineering technology, innovative tissue reconstruction protocols and transplantation techniques will continue to emerge into a new era of nanomaterials research.

Author Contributions

Xingrui Li and Yue Wang are co first authors, Yao Xiao and Jie Lei are the corresponding authors of this article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This publication of this review paper was supported by Sichuan Province Technology and Innovation Seedling Program (grant number 2021032), the Applied Basic Research of Luzhou Science and Technology Talent Bureau (grant number 2020-JYJ-40), and the National Undergraduate Innovation and Entrepreneurship Training Program of the Ministry of Education (grant number 202210632265), and Undergraduate Research Training at Southwestern Medical University School of Dentistry (grant numbe2022URTP02).

Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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