15	Gölz et al[12]	Human PDL	In vitro	Human primary PDLs were stimulated with lipopolysaccharide from *Porphyromonas gingivalis* (LPS-PG), a periodontal pathogenic bacterium, under normoxic and hypoxic conditions.	21% vs 1%	Quantitative PCR, immunoblots, immunostaining, and a specific ROS assay were performed to determine the levels of NOX4, ROS, and several redox systems. NOX4 and redox systems were evaluated using immunohistochemistry.	Significantly increased NOX4 levels were observed in PDL cells after hypoxic or inflammatory stimulation. Significant upregulation of ROS and catalase. The interaction of NOX4 and redox systems is crucial for ROS formation, which plays a pivotal role in oral diseases.
16	Zhou et al[16]	Human PDL	In vitro	PDLCs and DPCs were cultured under either normoxic (20% O_2) or hypoxic (2% O_2) conditions.	20% vs 2%	Cell viability assays were performed and the expression of pluripotency markers was detected using qRT-PCR and Western blotting. Mineralization, glycosaminoglycan (GAG) deposition, and lipid droplet formation were assessed using Alizarin red S, Safranin O, and Oil red O staining, respectively.	Hypoxia did not exert negative effects on the proliferation of PDLCs and DPCs. Hypoxia plays an important role in maintaining the stemness and differentiation capacity of PDLCs and DPCs.
17	Li et al[17]	Human PDL	In vitro	hPDLCs were cultured in the presence of 2% O_2 (hypoxia) or 20% O_2 (normoxia) and then subjected to a cyclic in-plane tensile deformation of 10% at 0.5 Hz.	20% vs 2%	1) Cell proliferation was analyzed using flow cytometry. 2) Cell ultrastructure was analyzed using transmission electron microscopy. 3) The expression of hypoxia-inducible factor-1α (HIF-1α) and osteogenic-related factor runt-related transcription factor 2 [RUNX2], and transcription	Significant increases in HIF-1α, SPP1, RUNX2, and SP7 expression occurred in cells cultured in the presence of hypoxia for 24 h. The MAPK inhibitor (PD 98,059) significantly attenuated hypoxia and cyclic tensile stress (CTS)-induced increases in phospho-ERK1/2 (extracellular regulated kinase 1/2), phospho-JNK (c-jun N-terminal kinase), and phospho-P38 levels. Hypoxia regulates CTS-responsive changes in the proliferation and osteogenic differentiation of

						factor Sp7 [SP7] were analyzed using RT-PCR and Western blotting. 4) The involvement of mitogen-activated protein kinase (MAPK) signaling pathways was investigated by treating cells with specific inhibitors and performing Western blotting.	hPDLCs by modulating MAPK pathways. Hypoxia-treated hPDLCs may represent an in vitro model to explore the molecular mechanisms of periodontitis.
18	Li et al[29]	Human PDL	In vitro	A periodontal ligament tissue model (PDLtm) was established by establishing 3-D cultures human PDLCs on a thin sheet of a poly lactic-co-glycolic acid scaffold. The PDLtm was treated with hypoxia and/or compression for 6, 24, or 72 h. The conditioned media were applied to cocultures of osteoblast and osteoclast (OC) precursors.	2%	RT-PCR was performed to analyze gene expression. Tartrate-resistant acid phosphatase staining was performed to examine OC formation.	Hypoxia significantly upregulated the expression of pro-osteoclastogenic cytokine genes in the PDLtm and increased osteoclastogenesis in the cocultures. The combination of compression and hypoxia exerted significantly stronger effects than either stimulus alone.
19	Kowalski et al[13]	Human anterior cruciate ligament	In vitro	Three novel anterior cruciate ligament (ACL)-derived cell populations with the potential for ligament regeneration were characterized. The proliferative and differentiation potential of ligament-forming fibroblasts, collagen gene expression and metabolism in cells cultured under both normoxic and hypoxic environments, and their trophic potential in vitro were examined.	20% vs 1%	Histology and immunohistochemistry Assessment of the potential for adipogenic, chondrogenic and osteogenic differentiation Gene expression analysis	Hypoxia induced significantly higher expression of both collagen I and III. Significantly increased GAG concentrations were detected in hypoxic cultures.

20	He et al[36]	Human PDL	In vitro	PDLSCs were separated and purified using the limiting dilution method and identified using flow cytometry. PDLSCs were cultured under hypoxic or normoxic conditions to observe their cloning efficiency.	20% vs 5%	PDLSC proliferation after exposure to different oxygen concentrations was evaluated using the MTT assay. Levels of proteins involved in the p38/MAPK and MAPK/ERK signaling pathways were detected using Western blotting. Inhibitors of p38/MAPK or ERK were applied to PDLSCs to observe their effects on clone formation and proliferation.	The proliferation of PDLSCs cultured under hypoxic conditions was higher than the control group ($P < 0.001$). A marked increase in p38 and ERK1/2 phosphorylation was observed in hypoxic PDLSCs compared to the control group ($P < 0.05$). Hypoxia increased PDLSC clone formation and proliferation by activating the p38/MAPK and ERK/MAPK signaling pathways.
21	Chen et al[18]	Human PDL	In vitro	Cells passaged to P4 were used in the experiments. The UCSC Genome Bioinformatics database was used to locate the HIF-1α, HIF1A-AS1 and HIF1A-AS2 Genes and to obtain the sequences of the HIF-1α, HIF1A-AS1 and HIF1A-AS2 mRNAs.	20% vs 2%	Western blot analysis ALP activity RT-qPCR	Expression levels of HIF1A-AS1, HIF1A-AS2, HIF-1α, and osteogenic biomarkers were increased in a time-dependent manner after exposure to hypoxia. HIF-1α exerted positive regulatory effects on HIF1A-AS1 and HIF1A-AS2. HIF-1α promoted the osteogenic differentiation of PDLCs, and HIF1A-AS2 exerted a negative effect on the osteogenic differentiation of PDLCs.
22	Giacoppo et al[10]	Human PDL	In vivo	The CM was collected from hPDLCs cultured under hypoxic conditions (H-hPDLSC-CM). Mice were anesthetized after EAE was induced in mice using myelin oligodendrocyte glycoprotein peptide (MOG).	20% vs 3%	- Immunofluorescence staining of mouse spinal cord tissues - Immunohistochemistry of mouse spinal cord tissues - Western blot analysis of mouse spinal cord tissues	A marked increase in the expression of IL-37 was observed in H-hPDLSC-CM-treated mice. In contrast, IL-17 and IFN-g expression was reduced after treatment with H-hPDLSC-CM Oxidative stress, autophagy, and apoptosis markers were detected in mice with EAE after hPDLSC-CM administration.

				Mice were randomly assigned to the following groups: 1) naive group (n = 5): mice did not receive an injection of $MOG_{35–55}$ or other drugs and were only used as controls; 2) EAE group (n = 15): mice were subjected to EAE with no other treatment; 3) EAE + H-hPDLSC-CM (n = 10): EAE mice were intravenously injected (tail) with H-hPDLSC-CM (1.0 mg/mouse) 14 d after EAE induction.		- -	
			In vitro	Murine-origin NSC-34 motoneuron cells mixed with 10% fetal bovine serum were cultured. Cells with a passage number of 30 were used in the present study. Cells were subsequently subjected to injury by creating manual scratches with a 1-ml pipette tip. After injury, the medium was removed, and cells were incubated with fresh serum-free medium for 24 h. Neuronal cells without scratch injury were also included as a control.	3%	Immunocytochemistry of NSC-34 neuron cells Western blot analysis of NSC-34 neuron extracts	Negative staining was observed for TNF-α, COX-2, and iNOS in injured neurons treated with H-hPDLSC- CM. A significant increase in the staining for the anti-inflammatory cytokine IL- 10 was observed in H-hPDLSC-CM-treated injured neurons H-hPDLSC-CM completely suppressed the activation of apoptosis. Western blot data reveal the presence of NT3, IL-10, and TGF-β in cells treated with H-hPDLSC-CM, suggesting a neuroprotective effect of H-hPDLSC-CM on injured neurons

23	Murabayashi et al[19]	Human PDL	In vitro	The properties of periodontal ligament-derived MSCs (PDLSCs) cultivated in serum-free and serum-containing media under hypoxic and normoxic conditions were characterized.	21% vs 3%	Cell growth, gene and protein expression, cytodifferentiation potential, genomic stability, cytotoxic response, and hard tissue generation by PDLSCs in vivo were examined.	Hypoxia did not alter the growth of PDLSCs under serum-free conditions but inhibited their osteogenic and adipogenic differentiation. PDLSCs cultured in serum-free culture media were more susceptible to damage following exposure to extrinsic cytotoxic stimuli than cells cultured in medium supplemented with serum.
24	Xiao et al[21]	Human PDL	In vitro	hPDLCs (4th passage) cultured using the tissue culture method were randomly assigned to slight (5% O_2), severe hypoxia (1% O_2), and control (21% O_2) groups.	1% and 5% vs 21%	The optical density values were detected, and the growth curve was constructed. A wound healing assay was performed to observe the migration of hPDLCs. RT-qPCR was conducted to detect the expression of cementum-related genes and Wnt signaling pathway-related genes. RT-qPCR, Western blot, and immunofluorescence staining were performed to detect HIF levels.	The growth rate of hPDLCs decreased as the O2 content decreased, and the morphology of hPDLCs changed in the presence of different O2 concentrations. hPDLCs migrate faster in 21% and 5% O2 than in 1% O2. The expression of cementum-related genes and Wnt signaling pathway-related genes increased in cells cultured under hypoxic conditions. The reduction in the O2 concentration increased the levels of the HIF messenger RNA and protein, and HIF was gradually transported from the cytoplasm into the nucleus in cells cultured with a 1% O2 concentration.
25	Ito et al[22]	Human PDL	In vitro	PDLC cultures were collected. For mRNA experiments and Western blotting, the cells were seeded onto six-well dishes at	Less than 0,1%	Quantitative reverse transcription PCR	PDL cells cultured under hypoxic conditions showed an increase in the expression of C/EBPβ and RANKL messenger RNAs (mRNAs).

				5.0 × 10^5 cells/well, and for small interfering RNA (siRNA) transfection experiments, the cells were seeded in 24-well dishes at 1.0 × 10^5 cells/well.		Expression of RANKL and HIf1 Secretion of cytokines from the PDL cells Expression of RANKL and HIF-1α proteins	Hypoxia did not alter the secretion of IL-1β, IL-6, IL-8, IL-17A, tumor necrosis factor-alpha, macrophage migration inhibitory factor, monocyte chemoattractant protein-1, and macrophage colony-stimulating factor in the culture media.
26	Kifune et al[34]	Human PDL Human embryonic fibroblasts (hEMBF)	In vitro	hPDLF (immortalized fibroblasts derived from human deciduous teeth) and hEMBF (immortalized fibroblasts obtained from a human embryo) were used in this study.	Less than 0.1%	The expression of the ANG, VEGF, stromal cell-derived factor-1 (SDF-1), and HIF-1α mRNAs was measured with a real-time RT-qPCR assay. Western blotting Cytokine array analysis	Levels of the ANG and VEGF mRNAs were significantly increased in PDL fibroblasts cultured under hypoxic conditions, but not in embryonic fibroblasts. Hypoxia increased the productions of ANG and VEGF proteins in PDL fibroblasts. The expression of the HIF-1α mRNA was not affected by hypoxia in either fibroblast line, although the level of the HIF-1α protein was increased after exposure to hypoxia. Under hypoxic conditions, HIF-1α upregulates synthesis of ANG and VEGF in PDL fibroblasts and promotes angiogenesis.
27	Liu et al[25]	Human PDL	In vitro	Hypoxia was induced by exposing cells to a tri-gas incubator with 3% O_2, cobalt chloride (CoCl2) was used to induce the stabilization of HIF-1α protein.	3%	qRT-PCR and Western blotting.	After treating PDLSCs with hypoxia (3% O2) over different time periods (0, 12, 24 and 48 h), qPCR results revealed that the transcription of *TGF"1* declined after 24 h and continued to decline after 48 h.
28	Yan et al[28]	Human PDL	In vitro	hPDLCs were extracted, cultured, and used between passages 3 and 6.	2%	- Real time PCR and Western blotting were performed to detect relative mRNA and protein levels.	Cells cultured in the presence of 2% O2 exhibited decreased A20 expression and an increased RANKL/OPG (R/O) ratio.

				hPDLCs were transfected with lentivirus A20 for overexpression or silencing studies. Twenty-four hours after transfection, 2.5 μg/mL puromycin was added and the cells were cultured for 24 h to select for positive cells.		- The formation of autophagosomes was measured using TEM. - Osteoclastic differentiation was assessed using TRAP staining and the hydroxyapatite resorption assay. The interactions between different proteins were observed using co-IP.	Autophagy in hPDLCs and osteoclast differentiation and hydroxyapatite resorption areas in mouse bone marrow mononuclear cells (BMMCs) were inhibited by A20. Moreover, A20 inhibited polyubiquitination at K63 and increased polyubiquitination at K48 of TRAF6 to suppress autophagy under hypoxic conditions.
29	Mao et al[30]	Human PDL	In vitro	Hypoxia shifted cell metabolism from oxidative phosphorylation to glycolysis with an accumulation of succinate in the cytosol and its release into culture supernatants.	1%	ALP and Alizarin Red S Staining.	The succinate supplement increased hPDLC proliferation, migration, and osteogenesis, but decreased succinate dehydrogenase (SDH) expression. The addition of the succinate supplement to cell cultures promoted intracellular succinate accumulation while stabilizing hypoxia inducible factor-1α (HIF-1α), leading to a state of pseudohypoxia. The succinate supplement altered cell metabolism in hPDLCs, induced a pseudohypoxia condition, and increased the proliferation, migration, and osteogenesis of mesenchymal stem cells in vitro.

CM, Conditioned medium

Abbreviations:

1.

a. CM Conditioned medium
b. DMEM Dulbecco's Modified Eagle's Medium, HG-DMEM: High-glucose DMEM
c. EV Extracellular vesicles
d. FBS Fetal Bovine Serum
e. LPS lipopolysaccharides
f. MCP Monocyte Chemotactic Protein
g. RANKL Receptor Activator of Nuclear Factor-kappa B
h. A20 TNF-α-induced protein 3 (TNFAIP3)
i. TRAF Tumor Necrosis Factor Receptor

j. EC Endothelial Cells
k. NS398 Cyclooxygenase 2 blocker
l. SU5416 Vascular Endothelial Growth Factor receptor inhibitor
m. VEGF Vascular Endothelial Growth Factor
n. PD98059 Extracellular Signal-regulated Protein Kinase [ERK] inhibitor
o. PGE_2 Prostaglandin E_2
p. BCK-2 B Cell Lymphoma 2
q. TEM Transmission Electron Microscopy
r. TRAP Tartrate-resistant Acid Phosphatase
s. Co-IP Coimmunoprecipitation
t. CCL2 CC chemokine ligand 2
u. IGFBP3 Insulin-like Growth Factor Binding Protein 3
v. MIF Macrophage Migration Inhibitory Factor
w. BIGH3 TGFβ in human clone 3
x. TR Thyroid Hormone Receptor
y. EAE Experimental Autoimmune Encephalomyelitis
z. *COX* *Cyclooxygenase*
aa. *iNOS* inducible Nitric Oxide Synthase
bb. GJIC Gap-junctional intercellular communication
cc. ANG Angiogenin
dd. *NOX4* NADPH Oxidase 4
ee. NAC N-acetylcysteine
ff. HIF-1α Hypoxia-inducible Factor-1α (HIF-1α)
gg. TGF-β Transforming Growth Factor-β1
hh. ELISA Enzyme-linked immunosorbent assay
ii. PCR Polymerase Chain Reaction, RT-qPCR: Real-Time Quantitative Polymerase Chain Reaction

2. Related to specific tendon/ligament:
   a. ACL Anterior Cruciate Ligament
   b. periodontal ligament stem cells PDLSCs
   c. IS Infraspinatus
   d. SDFT Superficial digital flexor tendon
   e. SL Suspensory ligament
   f. SS Supraspinatu