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# Unravelling the role of interleukin-6 in regulating dental stem cell behaviour: a scoping review

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## Abstract

**Background** Interleukin-6 (IL-6) functions as a pro-inflammatory and anti-inflammatory cytokine. IL-6 plays a pivotal role in a multitude of biological processes. This scoping review aimed to explore the impact of IL-6 on the biological responses of dental tissue-derived mesenchymal stem cells.

**Methods** The literature databases (PubMed and Scopus) were searched utilising specific design keywords. The criteria for inclusion encompassed (1) original research investigations that examined the effect of IL-6 on dental stem cells through the introduction of exogenous IL-6, overexpression, or knockdown expression, and (2) publications authored in the English language. The articles that conformed to these criteria were subsequently compiled for comprehensive full-text analysis and data extraction.

**Results** The literature search identified 323 articles, including 99 and 224 pertinent publications from the PubMed and Scopus databases, respectively. After screening, 14 publications satisfied the inclusion criteria and were subsequently selected for data extraction. The findings demonstrated that IL-6 regulates stemness maintenance, cellular proliferation, and differentiation towards osteogenic, adipogenic, chondrogenic, and neurogenic lineages in dental tissue-derived mesenchymal stem cells.

**Conclusion** IL-6 modulates the biological activities of mesenchymal stem cells, particularly those derived from dental tissues. Nevertheless, the inconsistencies observed across various studies may be attributable to a range of factors, including the heterogeneity inherent in stem cell sources, the stages of differentiation, the conditions of culture, and the particularities of experimental design.

**Keywords** Mesenchymal stem cells, Dental, Interleukin-6, Health

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## Introduction

Interleukin-6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory cytokine encoded by the *Il-6* gene in humans. It is a key member of the IL-6-type cytokine family, which includes ten members: IL-6, oncostatin M (OSM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotropin-1 (CT-1), cardiotrophin-like cytokine (CLC), neuropoietin (NP), IL-11, IL-27, and IL-31 [1, 2]. This multifunctional cytokine is secreted by various cell types, encompassing T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, and various tumour cell lines [1].

IL-6 is critical in numerous biological processes, including immune responses and bone metabolism [2, 3]. For instance, mice deficient in IL-6 exhibit impaired host defence mechanisms against bacterial infections, leading to significantly higher levels of proinflammatory cytokines compared to wild-type mice and a corresponding increase in mortality rates following experimental infections [4]. Moreover, IL-6 is known to be produced by osteoblasts, which stimulate the formation of osteoclasts both *in vitro* and *in vivo* [5, 6]. It also acts as a major cytokine in the central nervous system [7], and during tissue repair, stromal cells serve as a significant source of IL-6 [8]. Notably, targeting IL-6 signalling may have therapeutic potential in cancer, particularly as cancer stem cell-directed therapy [9]. When released by skeletal muscle cells, IL-6 acts as a myokine, a cytokine produced by muscle fibres in response to skeletal muscle cell differentiation [10]. Myokines have diverse functions, such as regulation of metabolism and inflammation.

Despite the well-documented effects of IL-6 on various cell types, its role in dental stem cells is still not fully understood. This scoping review focuses explicitly on the influence of IL-6 on the function of dental tissue-derived mesenchymal stem cells, with the aim of shedding light on its significance in oral biology.

## Methods

The articles were identified from the PubMed and Scopus databases from inception to Dec 15, 2024. These two databases were selected as primary sources due to their comprehensive coverage of biomedical research. PubMed search terms were (((“interleukin-6“[MeSH Terms] OR interleukin-6[Text Word])) AND ((“stem cells“[MeSH Terms] OR stem cells [Text Word]))) AND (((“dental pulp“[MeSH Terms] OR dental pulp[Text Word]) or (“periodontal ligament“[MeSH Terms] OR periodontal ligament[Text Word]) or (“tooth, deciduous“[MeSH Terms] OR deciduous teeth[Text Word])or (“dental papilla“[MeSH Terms] OR dental papilla[Text Word]) or (“gingiva“[MeSH Terms] OR gingiva[Text Word]))). The Scopus search terms were ABS ((“interleukin 6” OR “interleukin-6” OR “IL-6”) AND (stem AND cell) AND (“dental pulp” OR “periodontal ligament” OR “tooth, deciduous” OR “dental papilla” OR “gingival”)). The title and abstracts were carefully screened to select the relevant studies regarding the effect of IL-6 on dental stem cells. The inclusion criteria were (1) original research studies investigating the effect of IL-6 on dental stem cells by adding exogenous, overexpression, or knockdown expression of IL-6, and (2) publications in English. The exclusion criteria were (1) review articles, (2) studies unrelated to dental stem cells, and (3) studies not investigating the effects of IL-6. The included articles were collected for full-text analysis and data extraction (Fig. 1).

## Results

The literature search yielded 323 articles comprising 99 and 224 relevant publications from the PubMed and Scopus databases. After screening, 14 publications met the inclusion criteria and were further included for data extraction. Detailed information from each study was extracted in Table 1 and Supplementary Table 1.

## Discussion

### IL-6 signalling

IL-6 is a glycosylated cytokine with a four-helix bundle structure. Two forms of IL-6 receptor (IL-6R) have been identified as membrane-bound and soluble forms [11]. IL-6 binds to the IL-6 receptor, and this complex subsequently associates with glycoprotein 130, forming a hexameric structure composed of 2 molecules each of IL-6, IL-6R, and gp130 [12]. This complex then further activates intracellular signal transduction [13]. Alternatively, there is another activation called trans-signalling through the function of a soluble form of the IL-6R (sIL-6R). sIL-6R can be generated by proteolytic cleavage of mIL-6R by the metalloproteinase TNFα-converting enzyme (TACE; ADAM17) and ADAM10. Another method is an alternatively spliced IL-6 mRNA [14, 15]. sIL-6R binds to IL-6 and further binds to gp130 on those cells that do not express mIL-6R, leading to the activation of an intracellular signalling cascade [16].

Three major signalling pathways downstream of the IL-6 receptor complex have been identified: JAK/STAT, MAPK, and PI3K/Akt (Fig. 2). The primary intracellular pathway for IL-6 is the JAK/STAT signalling. Upon forming a hexameric complex, the JAK associated with gp130 becomes activated and phosphorylated. The phosphorylated gp130 cytoplasmic tails, using the SH2 domain, bind the Signal Transducers and Activators of Transcription protein (STAT), leading to the phosphorylation of STAT protein, especially STAT3 [17]. The phosphorylated STAT3 forms the dimers, translocates to the nucleus, and subsequently binds to specific DNA

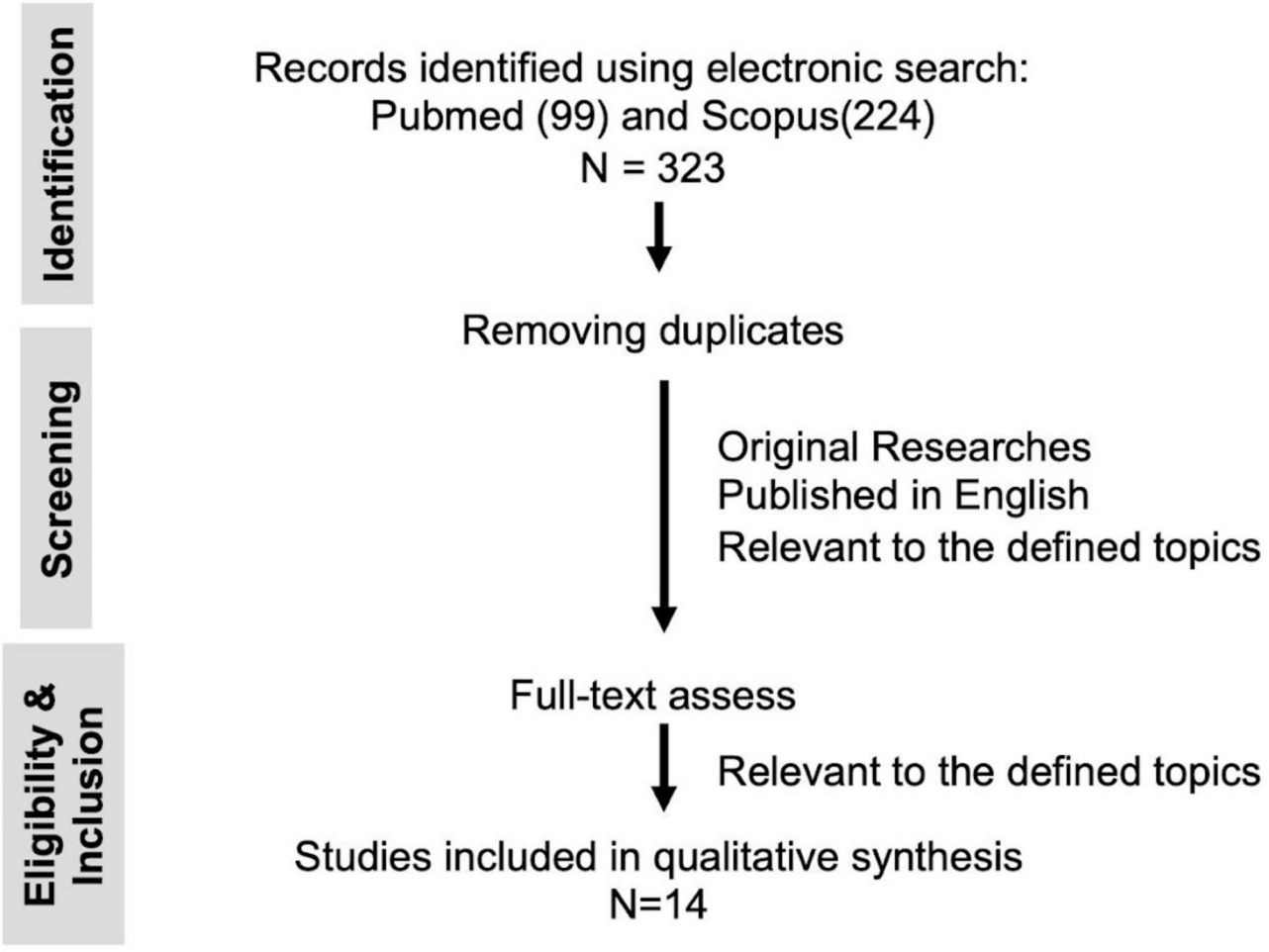


**Fig. 1** Search flow chart from identification to included studies

**Table 1** The effects of IL-6 on dental stem cell behaviours

| Cell Types | Finding | References |
|---|---|---|
| Stem cells isolated from human exfoliated deciduous teeth (SHEDs) | IL-6 treatment promoted pluripotent stem cell marker expression. | Govitvattana et al., 2013 [64]; Govitvattana et al. 2015 [65]; Nowwarote et al., 2017 [66] |
| | IL-6 promoted mineralization. | Nowwarote et al., 2018 [67] |
| | Endothelial cell-secreted IL-6 is involved in the maintenance of the perivascular niche. | Oh et al., 2020 [76] |
| Human dental pulp stem cells (DPSCs) | IL-6 cytokine family promoted osteogenic differentiation. | Park et al. 2019 [70]; Feng et al., 2016 [69]; Kang et al., 2022 [77] |
| | IL-6 attenuated osteogenic, chondrogenic, and adipogenic differentiation. | Kaplan et al., 2023 [71] |
| | IL-6 inhibited neuronal differentiation. | Park et al. 2019 [70] |
| | IL-6 released by human dental pulp stem cells promoted M2 macrophage polarization. | Liu et al., 2023 [75] |
| | Endothelial cell-secreted IL-6 is involved in the maintenance of the perivascular niche. | Oh et al., 2020 [76] |
| Human periodontal ligament stem cells (PDLSCs) | IL-6 promoted osteogenic differentiation. | Purwaningrum et al., 2023 [68] |
| | IL-6 released by mechanically loaded human periodontal ligament stem cells promoted osteoclast formation. | Luo et al., 2024 [78] |
| | IL-6 participated in D-mannose-enhanced immunomodulation. | Guo et al., 2018 [79] |
| | IL-6 released by human periodontal ligament stem cells reduced polymorphonuclear neutrophil apoptosis | Wang et al., 2017 [80] |

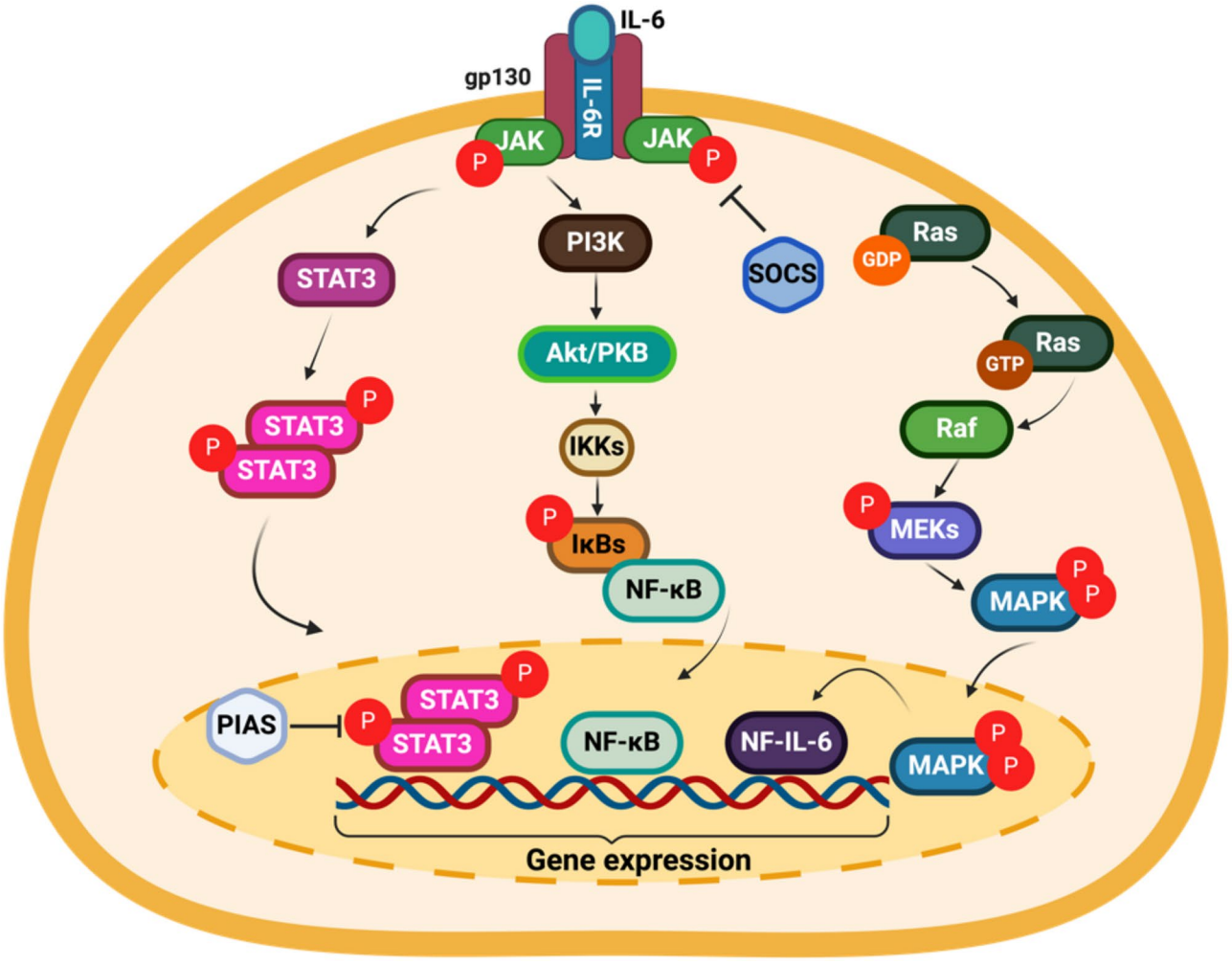


**Fig. 2** Intracellular signalling pathways of IL-6

response elements, regulating the target gene transcription [17]. However, it was noted that IL-6 upregulated both STAT1 and STAT3.

IL-6 regulates cell responses through the MAPK and PI3K/Akt pathways. In bone marrow-derived mesenchymal stem cells, IL-6 promotes survival under serum starvation and inhibits adipogenic differentiation via ERK1/2 activation, independent of JAK/STAT signalling [18]. IL-6 also activates p38 MAPK, influencing stress and inflammation responses. Additionally, IL-6 enhances cell survival by upregulating cyclin D1 via PI3K/Akt in prostate cancer cells [19] and promotes cardiac differentiation through PI3K signalling, affecting PKC, PTEN, and Akt phosphorylation [20]. The activation of these downstream signalling by IL-6 leads to multiple cellular responses.

### Biological functions of Interleukin-6

IL-6 is a multifunctional cytokine produced by diverse cell types, such as lymphocytes, endothelial cells, fibroblasts, muscle cells and epithelial cells [10, 21]. IL-6 has been regarded as possessing both pro-inflammatory and anti-inflammatory properties [22].

IL-6 regulates numerous vital biological processes, including immune response, inflammation, haematopoiesis, and cell differentiation [23]. IL-6 has a critical role in immune regulation and inflammation. IL-6 signalling is a crucial element of inflammation and repair in health and seems to support a central role in the pathogenesis of inflammatory diseases. IL-6 was originally identified as T cell-derived lymphokine that induces the final maturation of B cells into antibody-producing cells [24]. Macrophages can secrete IL-6 in response to specific microbial molecules [25]. IL-6 modulates the adaptive immune response by promoting T helper 2 phenotypes but inhibiting T helper 1 polarisation [26]. IL-6 induces CD4 + T cells to produce IL-4, driving differentiation towards the Th2 lineage [27]. On the contrary, IL-6 decreased interferon-gamma production by CD4 + T lymphocytes, which in turn reduced T cell activation [28].

IL-6 plays a pivotal role in maintaining bone homeostasis. Research has demonstrated that IL-6 promotes the formation and activity of osteoclasts. It regulates the expression of RANK in preosteoclasts and osteoclasts [29]. The IL-6/sIL-6R complex induces osteoclast differentiation in murine bone marrow-derived macrophages, with its effects varying by RANKL concentration enhancing osteoclastogenesis at low RANKL (10 ng/mL) but inhibiting it at high RANKL (50 ng/mL) [30]. Furthermore, IL-6-induced RANKL expression in osteoblasts stimulates osteoclast formation via the JAK2/STAT3 pathway [31].

Concerning its impact on bone cells, IL-6 and IL-6R mRNA expression levels were increased during osteogenic induction of bone marrow-derived mesenchymal stem cells [32]. Adding IL-6 or sIL-6R to the induction medium promoted osteogenic differentiation, as seen by increased osteogenic marker expression, alkaline phosphatase activity, and mineral deposition [32]. Similar results were observed in periodontal ligament cells in which IL-6/sIL-6R enhanced alkaline phosphatase enzymatic activity and Runx2 expression, potentially via IGF-I production [33]. IL-6 treatment decreased *SOX2* expression but increased *RUNX2* and *DLX5* expression, suggesting IL-6-induced osteogenic lineage commitment [34].

IL-6 is a critical regulator in the control of cell differentiation. In addition to promoting osteogenic differentiation, IL-6 also influences the differentiation of cells along various lineages. For instance, studies have demonstrated that IL-6 stimulates the proliferation of human epidermal keratinocytes and induces the reorganisation of their keratin cytoskeleton [35]. IL-6 modulates the myogenic differentiation depending on concentration; low concentration of IL-6 inhibits while high IL-6 concentration promotes MyoD and myogenin expression, regulating myogenic differentiation in myofibroblast cells [36].

In embryonic stem cells, the addition of IL-6 resulted in the enhancement of NKX2.5 and GATA4 expression, transcriptional factors regulating cardiac lineage commitment [20]. IL-6/sIL-6R complex markedly enhanced the neural differentiation of neural stem cells derived from human induced pluripotent stem cells [37]. STAT3 inhibition resulted in less ramified neuronal cells [37]. However, a study in neural stem cells indicated that IL-6 inhibited neural differentiation but promoted glial cell differentiation in a dose-dependent manner as determined by the expression of NeuN and GFAP, respectively [38]. This regulation was also modulated via the JAK2/STAT3 pathway [38]. Collectively, these findings highlight the regulatory role of IL-6 in controlling the differentiation of stem cells into various lineages.

Interestingly, IL-6 has crucial roles in wound healing, probably by regulating leukocyte infiltration, angiogenesis, and collagen accumulation [39]. Neutralizing IL-6 delayed wound closure in murine skin wounds, while IL-6 deficiency led to impaired leukocyte infiltration, re-epithelialization, angiogenesis, and collagen accumulation in mice experiments [39]. IL-6 promoted the mRNA and protein expression of those molecules related to angiogenesis in myofibroblasts, including ICAM-1, VCAM-1, and vascular endothelial growth factor. Further, IL-6 treatment enhanced endothelial cell migration and vessel-like structure formation [40]. In aortic ring assays, IL-6 induced vascular sprouting and lung endothelial cell migration via STAT3, akin to VEGF-mediated effects through ERK [41]. Further, IL-6 is involved in extracellular matrix synthesis, a crucial process during wound healing. IL-6 treatment upregulated the *COL1A1*, *COL2A1*, and *COL3A1* mRNA expression in tendon fibroblast cells via TGF signalling [42]. Taking the aforementioned data together, IL-6 exhibits a multifaceted role in regulating tissue repair and regeneration processes through its effects on various cell types and signalling pathways.

#### Interleukin-6 and mesenchymal stem cells

IL-6 was originally identified in the immune system as a multifunctional cytokine. It was also found that IL-6 is important in stem cell maintenance, proliferation, and differentiation in several tissues [12]. Endogenous IL-6 binds to IL6Rs on cortical precursors to promote their self-renewal and maintain their numbers during embryogenesis [43]. However, in embryonic stem cells, the expression levels of IL-6 were low. Addition of IL-6 after day 4 induced pluripotent stem cells at the onset of iPS reprogramming [44]. Leukaemia inhibitory factor (LIF) is a member of the IL-6 cytokine family and is known to maintain stemness in mouse pluripotent stem cells. IL-6/sIL-6R could also support stemness maintenance in rat embryonic stem cells, similar to LIF [45]. IL-6/sIL-6R promoted neurogenic and glial differentiation of human induced pluripotent stem cell-derived neural stem cells as determined by the expression of neuronal nuclei, RNA binding protein fox-1 homolog three and glial fibrillary acidic protein [46]. In addition, STAT3 inhibition could attenuate these effects [46]. On the contrary, IL-6 suppressed neurogenic differentiation in murine embryonic stem cells but enhanced oligodendrocyte differentiation and maturation [47, 48]. The available data suggest a critical role for IL-6 in the function of pluripotent stem cells. For mesenchymal stem cells, IL-6 participates in the modulation of several functions of mesenchymal stem cells, including immunomodulatory effects, differentiation potency, cell proliferation and migration.

#### *IL-6 and mesenchymal stem cell proliferation*

IL-6 enhanced human bone marrow-derived mesenchymal stem cell proliferation via ERK1/2 signalling [18]. In this regard, exogenous IL-6 significantly increased while siRNA IL-6 reduced cell number [18, 49]. Silencing the endogenous expression of IL-6 in human bone marrow-derived mesenchymal stem cells resulted in a significant decrease in the S/G2/M cell population, accompanied by a reduction in Ki-67-positive cells and cyclin D1 expression [49]. This effect was mediated through the ERK1/2 signalling pathway [49]. Similarly, exogenous IL-6 significantly increased cell proliferation and colony-forming unit in endometrial mesenchymal stem-like cells, potentially via the Wnt pathway [50]. On the contrary, IL-6 did not significantly alter cell proliferation in human and murine bone marrow-derived mesenchymal stem cells [51, 52]. Further, IL-6 protects human bone marrow-derived mesenchymal stem cells from apoptosis during serum starvation as determined by the reduction of TUNEL-positive cells and apoptotic-related gene expression [18]. In addition, bone marrow-derived mesenchymal stem cells exhibited a lesser number of senescence cells when treated with neutralised antibodies against IL-6 [53]. Correspondingly, bone marrow-derived mesenchymal stem cells from IL-6 knockout mice exhibit a greater number of senescence cells when exposed to exogenous IL-6 [53]. The impact of IL-6 on mesenchymal stem cell proliferation remains inconclusive. Further research is required to elucidate this relationship.

#### *IL-6 and mesenchymal stem cell differentiation*

The role of IL-6 on mesenchymal stem cell differentiation has been extensively studied. The influence of IL-6 on osteogenic differentiation by human bone marrow-derived mesenchymal stem cells was not robust [52]. IL-6 treatment slightly enhanced *in vitro* mineral deposition and osteogenic marker gene expression, but no significant difference was observed [52]. On the contrary, IL-6 or sIL-6R supplementation in an osteogenic medium increased alkaline phosphatase enzymatic activity by human bone marrow-derived mesenchymal stem cells [54]. The combination of IL-6 and sIL-6R led to the additional upregulation of ALP activity compared with either IL-6 or sIL-6R treatment alone [54]. Further, IL-6/sIL-6R promoted *in vitro* mineralisation by human adipose stem cells via STAT3 and ROR/Wnt pathway [55].

IL-6 was upregulated during chondrogenic differentiation by human mesenchymal stem cells (hMSCs), corresponding with the expression of IL-6R. IL-6 peaked at day 3 after chondrogenic induction and decreased thereafter [56]. In comparison, IL-6R peaked on day 7 [56]. IL-6 and IL-6R supplementation resulted in the enhancement of chondrogenic differentiation as determined by the significant increase in pellet size and expression of chondrogenic marker genes (*COL2A1*, *ACAN*, and *COL10A1*) [56]. This phenomenon was attenuated by siRNA against STAT3 [56]. The opposite effect was observed in murine bone marrow-derived mesenchymal stem cells. In this regard, IL-6-treated mBM-MSCs reduced pellet size and proteoglycan production in a dose-dependent manner [51].

The adipogenic differentiation of human mesenchymal stem cells was promoted by IL-6 treatment. In this regard, the expression of IL-6 and its receptor, IL-6R, increased during the adipogenic differentiation of mesenchymal stem cells [57]. Furthermore, knockdown IL-6R using siRNA or IL-6 overexpression using shRNA demonstrated a positive correlation between the expression of IL-6R and the adipogenic differentiation of mesenchymal stem cells, which is shown to be regulated via the phosphorylation of p38 MAPK [57]. IL-6 knockout mice demonstrated a reduction in the percentage of tibia adiposity and adipocyte number in bone marrow compared to wild-type mice [53]. In the context of neuronal differentiation, anti-IL-6R antibody treatment with transplant bone marrow stromal cells promotes neurotrophic factor release and decreases apoptosis in the transplanted cells [58].

#### *IL-6 and Immunomodulatory effects of mesenchymal stem cells*

Mesenchymal stem cells exert a regulatory influence on macrophage polarisation via IL-6/STAT3 signalling. In this regard, co-culturing macrophages with preconditioned mesenchymal stem cells results in a marked reduction in M1 markers but an increase in the expression of M2b markers [59]. IL-6 is involved in human mesenchymal stem cells mediated inhibition of activated T-cell proliferation [49]. The shRNA targeting IL-6 in mesenchymal stem cells led to the induction of T-cell proliferation in a dose-dependent manner [49]. Silencing IL-6 expression in human decidua-derived mesenchymal stromal cells decreased the expression of PD-L1 and PD-L2, which are important immune checkpoints [60]. IL-6 supplementation rescues the effect of PD-L1 and PD-L2 inhibition in IL-6 knockdown cells [60]. Co-culturing of peripheral blood mononuclear cells and IL-6 knockdown decidua-derived mesenchymal stromal cells resulted in a higher percentage of Ki67 + T-cells and IFN-gamma + T cells compared to those co-cultured with control mesenchymal stromal cells [60]. It has also been shown that IL-6 mRNA expression decreased during the differentiation of mesenchymal stem cells, which is associated with leucocyte-mediated cell death in an allogeneic leucocyte co-culture study [61]. Adding exogenous IL-6 partially rescued the allogeneic cells from this leucocyte-mediated cytotoxicity [61], implicating IL-6 roles in immunomodulation by mesenchymal stem cells.

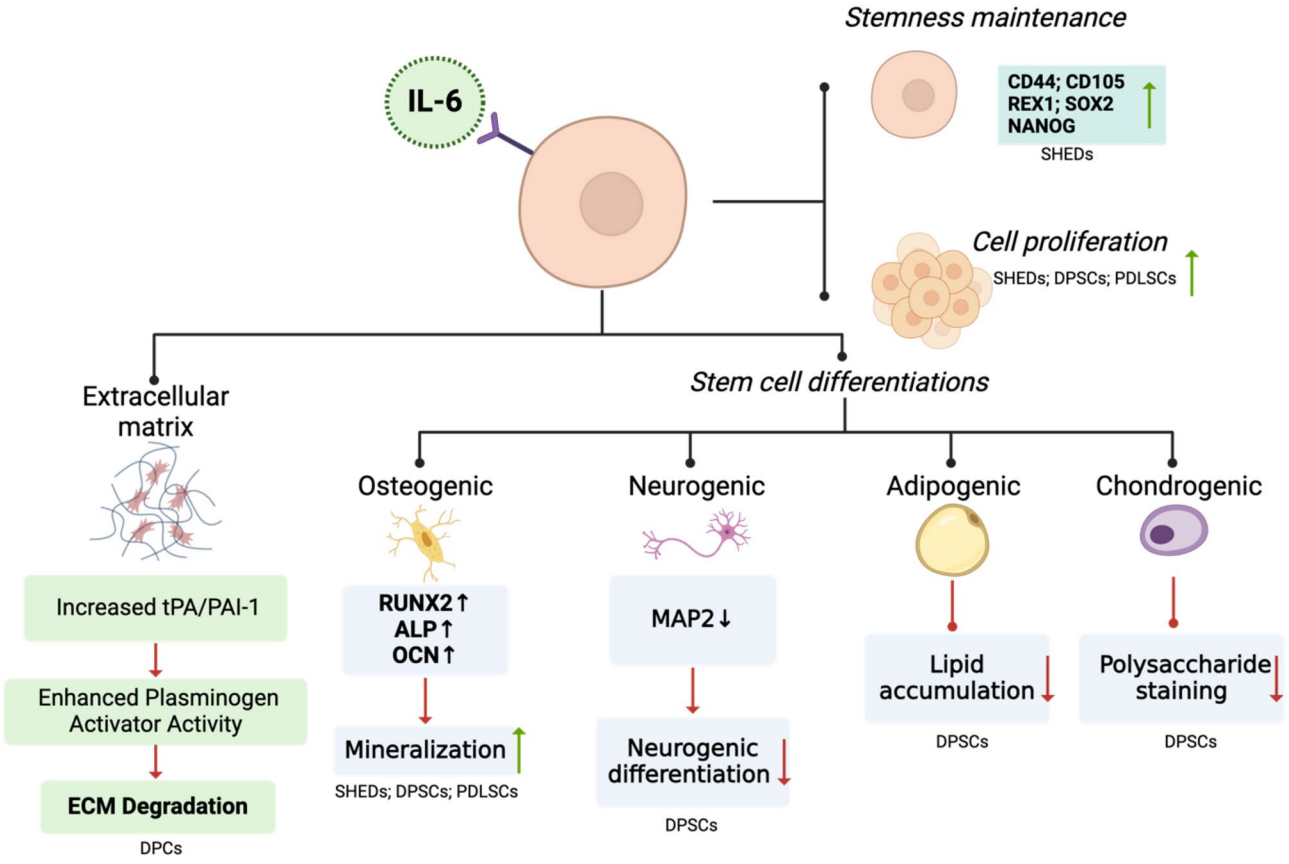


**Fig. 3** Schematic diagram demonstrates the role of IL-6 in the control of dental tissue-derived mesenchymal stem cells. SHEDs; stem cells isolated from human exfoliated deciduous teeth, DPSCs; dental pulp stem cells, PDLSCs; periodontal ligament stem cells. Created by biorender.com

### *IL-6 and mesenchymal stem cell migration*

IL-6 regulates the migration of mesenchymal stem cells. Mesenchymal stem cells demonstrated a strong migratory response toward IL-6 [62]. The addition of IL-6 also facilitated cell migration from three-dimensional spheroid derived from mesenchymal stem cells [62]. This increased migratory effect could also be modulated by the influence of IL-6 on extracellular matrix homeostasis. In this regard, mesenchymal stem cells increased MMP1 and MMP3 expression as well as the inhibitor, TIMP1, expression at 24 h after IL-6 stimulation in two-dimensional culture [62]. On the contrary, in three-dimensional spheroid culture, IL-6 treatment caused significant upregulation in MMP8 and TIMP4 [62]. Skin-mesenchymal stem cells isolated from IL-6 knockdown mice exhibited a defective cell migration capacity compared to those from wild-type counterparts [63]. The addition of recombinant IL-6 rescued this attenuated effect. In addition, the cell index was significantly higher in those skin-mesenchymal stem cells from IL-6 knockdown, implicating the defect in cellular contraction. This evidence underlines the crucial role of IL-6 in mesenchymal stem cell migration [63].

### IL-6 and dental tissue-derived stem cells

Interestingly, IL-6 regulates several biological processes in dental tissue-derived mesenchymal stem cells (Fig. 3). IL-6 was found to play a role in maintaining the stemness of human exfoliated deciduous teeth [64–66]. For example, IL-6 treatment increased pluripotent marker REX1 expression in stem cells isolated from human exfoliated deciduous teeth [66]. This effect could be inhibited by a JAK inhibitor or a P2Y1 antagonist [64, 65], suggesting the involvement of the JAK and ATP-P2Y1 signalling pathway. IL-6 dramatically enhanced pluripotent (*NANOG*, *SOX2*, and *REX1*) and mesenchymal stem cells (*CD44* and *CD105*) marker expression in stem cells isolated from human exfoliated deciduous teeth [67].

Furthermore, there was no evidence that IL-6 treatment influenced the proliferation of stem cells isolated from human exfoliated deciduous teeth, as determined by MTT assay and colony forming unit assay [67]. Similar effects of IL-6 on cell proliferation were observed in human periodontal ligament stem cells and human dental pulp stem cells [68, 69].

IL-6 supplementation in osteogenic culture medium significantly promoted mineralisation in stem cells isolated from human exfoliated deciduous teeth at day 14

[67]. *ALP*, *ANKH*, and *PIT1* mRNA levels were markedly increased in IL-6-treated conditions, while other osteogenic differentiation markers were not altered [67]. Correspondingly, IL-6 enhanced the osteogenic differentiation of human dental pulp stem cells, as confirmed by the increased mineralisation and the expression of osteogenic markers RUNX2 and OCN [70]. Further, the inflamed dental pulp stem cells have superior ability in osteogenic differentiation via the function of IL-6 as the neutralisation of IL-6 attenuated the mineral deposition and RUNX2 protein expression [70]. Oncostatin M, a member of the IL-6 cytokine family, has been shown to promote osteogenic differentiation in human dental pulp stem cells through the JAK3 signalling pathway [69]. Specifically, the supplementation of oncostatin M at a concentration of 10 ng/mL resulted in a significant increase in alkaline phosphatase enzymatic activity, *in vitro* mineral deposition, and the expression of osteoblast-related markers such as ALP, OCN, BMP-2, and RUNX2 [69]. Similar effects were also observed in human periodontal ligament stem cells, in which IL-6 enhanced ALP enzymatic activity, osteogenic marker gene expression, and in vitro mineral deposition in a dose-dependent manner [68]. Mechanistically, IL-6 promoted *WNT2B*, *WNT10B*, and *WNT5A* expression. The chemical inhibition for canonical and non-canonical Wnt signalling attenuated the IL-6-induced osteogenic induction. Correspondingly, the knockdown of *WNT2B*, *WNT10B*, and *WNT5A* resulted in decreased osteogenic marker gene expression and mineralisation. At the same time, supplementation with recombinant WNT2B, WNT10B, and WNT5A enhanced osteogenic differentiation ability, implying the involvement of the Wnt pathway in IL-6-induced osteogenic differentiation in human periodontal ligament stem cells [68]. A study in human periodontal ligament cells also demonstrated similar results. IL-6 and its soluble receptors increased alkaline phosphatase enzymatic activity by the regulation of MAP and JAK pathways [33]. On the contrary, Kaplan et al. reported that IL-6 significantly inhibits osteogenic differentiation in human dental pulp cells, as evidenced by the reduction of calcium deposition [71].

IL-6 did not affect neurogenic differentiation in stem cells isolated from human exfoliated deciduous teeth [67]. However, in human dental pulp stem cells, IL-6 inhibited neurogenic differentiation, as confirmed by the reduction of MAP2 and NeuN expression in IL-6-treated conditions [70]. For adipogenic differentiation, IL-6 did not affect the adipogenic differentiation of stem cells isolated from human exfoliated deciduous teeth [67]. In contrast, IL-6 significantly inhibited the adipogenic differentiation of dental pulp stem cells, as evidenced by reduced intracellular lipid accumulation [71]. This discrepancy could be due to the different sources of dental stem cells. Lastly, IL-6 treatment led to the reduction of acidic polysaccharides accumulation, visualised by the decreased staining of alcian blue, indicating the inhibition of chondrogenic differentiation [71]. Thus, the effects of IL-6 on the multilineage differentiation potential of dental stem cells appear to be complex, potentially influenced by stem cell types, microenvironment, and differentiation lineages.

Natural antioxidants like curcumin and ascorbic acid help reduce inflammation and oxidative stress in dental pulp stem cells Curcumin, in liposome form, inhibits the NFκB/ERK/pERK pathway, lowering pro-inflammatory cytokines (IL-6, IL-8, MCP1, IFNγ) in HEMA-treated dental pulp stem cells. Similarly, ascorbic acid reduces ROS production, downregulates inflammatory pathways, and decreases IL-6 levels. These antioxidants may aid dental pulp regeneration by modulating inflammation and promoting cell homeostasis [72, 73].

In addition to its roles in maintaining stemness and regulating differentiation potential, IL-6 may also contribute to the homeostasis of the extracellular matrix. Specifically, IL-6 treatment has been shown to significantly enhance plasminogen activator activity in human dental pulp cells in a time- and concentration-dependent manner. Furthermore, the mRNA expression levels of tissue-type plasminogen activator and plasminogen activator inhibitor-1 were elevated in human dental pulp cells upon exposure to IL-6, suggesting a potential involvement of IL-6 in regulating extracellular matrix degradation [74].

The findings on IL-6's role in dental tissue-derived stem cells have significant clinical implications for regenerative dentistry and tissue engineering. IL-6's ability to enhance osteogenic differentiation suggests its potential application in bone regeneration therapies, particularly for treating bone defects, periodontitis, and implant osseointegration. Studies demonstrate that IL-6 increase ALP activity, Runx2 expression, and mineral deposition in periodontal ligament stem cells and dental pulp stem cells [33, 68, 70]. However, conflicting reports indicate that IL-6 may inhibit osteogenesis in certain contexts, highlighting the need for further optimal dosing and delivery methods [71].

Beyond bone regeneration, IL-6 is crucial in maintaining stemness in dental tissue-derived stem cells, essential for stem cell-based therapies. In stem cells from human exfoliated deciduous teeth, IL-6 upregulates pluripotency markers (*NANOG*, *SOX2*, *REX1*) and mesenchymal markers (*CD44*, *CD105*) [64–67]. This property could enhance cell culture techniques, allowing for more significant expansion of therapeutic cell populations without losing their differentiation capacity. Furthermore, IL-6 has been shown to reduce age-related decline in bone marrow-derived mesenchymal stem cells, suggesting potential anti-ageing applications for dental stem cells

as well [53]. The ability to extend the stemness in culture could improve in vitro culture for stem cells in clinical therapeutic applications.

IL-6 also contributes to wound healing and periodontal tissue regeneration by promoting angiogenesis, extracellular matrix remodelling, and leukocyte recruitment [39, 40]. IL-6 enhances plasminogen activator activity in dental tissue-derived stem cells, facilitating extracellular matrix degradation and tissue repair [74]. Furthermore, IL-6 upregulates collagen (COL1A1, COL3A1) and matrix metalloproteinases in fibroblasts, which are critical for gingival and pulp regeneration [42]. Combining IL-6 with anti-inflammatory agents may further enhance tissue repair by modulating inflammation [72, 73]. Hence, further development of delivery systems for IL-6 in vital pulp therapy may facilitate dental pulp tissue healing and reduce inflammation, leading to the promotion of dentin bridge formation.

Another key clinical application of IL-6 is in its immunomodulatory effects. IL-6 influences macrophage polarisation and T-cell proliferation, which may improve the success of stem cell transplants [59, 60], making room for using IL-6 in whole pulp tissue transplantation for potential regenerative endodontic application. Although preclinical studies show IL-6's potential in stem cell therapy and tissue repair, more research is needed to confirm its effectiveness, refine treatment methods, and evaluate safety before human use.

## Conclusion

In conclusion, IL-6 plays a crucial role in regulating the biological activities of mesenchymal stem cells, including dental stem cells. IL-6 modulates the maintenance of stem cell properties, regulation of cell proliferation and migration, modulation of multi-lineage differentiation potential, and regulation of immunomodulation. The main intracellular signalling includes JAK/STAT, MAPK, and PI3K pathways. However, the discrepancy observed across different studies could be due to several factors, including the heterogeneity of stem cell sources, differentiation stages, culture conditions, and specific experimental designs. Further studies are required to fully elucidate the underlying molecular mechanisms by which IL-6 exerts its effects on dental stem cells, which may provide important insights into developing IL-6-based therapeutic strategies for regenerative dentistry.

### Abbreviations

| | |
|---|---|
| IL-6 | Interleukin-6 |
| OSM | Oncostatin M |
| LIF | Leukaemia inhibitory factor |
| CNTF | Ciliary neurotrophic factor |
| CT-1 | Cardiotropin-1 |
| CLC | Cardiotrophin-like cytokine |
| NP | Neuropoietin |
| IL-6R | Interleukin-6 receptor |
| STAT | Signal Transducers and Activators of Transcription protein |
| LIF | Leukaemia inhibitory factor |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-025-06097-w.

Supplementary Material 1

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### Author contributions

IA contributed to conceptual design and manuscript drafting. NN contributed to data extraction and manuscript drafting. SP contributed to figure formulation and data extraction. WD and LS contributed to data analysis and critical editing of the manuscript. TO contributed to project management, conceptual design, data acquisition, data extraction, and critical editing of the manuscript.

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### Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used generative artificial intelligence tools to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

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