Secretome Derived from SHED in Tissue Regeneration

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Stem cells from human exfoliated deciduous teeth (SHED) have emerged as an alternative stem cell source for cell therapy and regenerative medicine because they are readily available, pose fewer ethical concerns, and have low immunogenicity and tumourigenicity. SHED offer a number of advantages over other dental stem cells, including a high proliferation rate with the potential to differentiate into multiple developmental lineages. The therapeutic effects of SHED are mediated by multiple mechanisms, including immunomodulation, angiogenesis, neurogenesis, osteogenesis, and adipogenesis. Since SHED are more potentially useful source of stem cells than BM-MSCs and DPSCs in cell therapy, therefore it could be suggested that the secretome derived from SHED could enhance tissue regeneration and repair and hence, considered as a suitable candidate for a cell-free approach in regenerative medicine and dentistry.

secretome conditioned medium SHED

1. Introduction

The secretome derived from stem cells from human exfoliated deciduous teeth (SHED) or preferably called conditioned medium (SHED-CM) in a number of studies, can stimulate various biological activities in different cell types in vitro as well as in vivo through complicated processes. In most studies, the SHED-CM was prepared by collecting the medium from SHED cultured for at least 48 h in serum-free supplemented media, usually Dulbecco's Modified Eagle's medium (DMEM). The SHED-CM was then centrifuged to remove all cell debris. The supernatant from SHED-CM obtained during centrifugation was usually used without enrichment or dilution for subsequent experimental analyses.

Studies have shown that the secretome derived from SHED holds great potential as a therapeutic agent for various diseases and injuries related to tissue regeneration and has been shown to play significant roles in proliferation, apoptosis, angiogenesis, osteogenesis, chondrogenesis, immunomodulation, and immunoregulation in many pathological conditions.

2. Effect of SHED-Derived Secretome on Proliferation and Apoptosis

Much evidence has revealed the remarkable ability of SHED-derived secretome to promote proliferation and inhibit apoptosis. In a mouse model of perinatal hypoxia–ischemia (HI)-induced brain injury, SHED-CM exhibited significant reductions in apoptosis and tissue loss [1]. Additionally, in a mouse model of streptozocin-induced diabetes, SHED-CM has been shown to promote the proliferation of pancreatic β-cells and enhance insulin secretion [2].

Yamaguchi et al. (2015) showed that SHED-CM exhibited a significant suppressive effect on apoptosis in a mouse model of ischemic heart, as evidenced by a remarkable reduction in TUNEL-positive cardiomyocytes compared to untreated mice [3]. Matsushita et al. (2017) discovered that SHED-CM secreted various tissue-regenerating factors known for their roles in antiapoptosis and hepatocyte protection, as well as in the proliferation and differentiation of liver progenitor cells [4].

3. Effect of SHED-Derived Secretome on Immunomodulation and Immunoregulation

Several studies revealed that the secretome derived from SHED has a therapeutic effect through its immunomodulatory and anti-inflammatory actions. Matsubara et al. (2015) discovered that SHED-CM exhibited immunomodulatory and anti-inflammatory effects characterised by a reduction in proinflammatory cytokine levels and induction of M2 anti-inflammatory macrophages in a rat model of spinal cord injury (SCI) [5]. These effects led to a remarkable recovery of hindlimb locomotor function. Wakayama et al. (2015) demonstrated that SHED-CM significantly suppressed the mRNA expressions of TNF-α, IL-6, IL-1β, and iNOS while simultaneously upregulating the expressions of M2 cell markers in bleomycin (BLM)-induced acute lung injury (ALI) in mice [6]. The study also confirmed the ability of SHED-CM to induce M2 differentiation in bone marrow-derived macrophages through in vitro experiments.

Similar findings were also reported by other studies, in which SHED-derived secretome exhibited a potent anti-inflammatory effect in both a rat model of acute liver failure (ALF) [4] and a mouse model of ischemia-reperfusion (I/R) [3]. In a mouse model of autoimmune encephalomyelitis, SHED-CM demonstrated its ability to suppress proinflammatory cytokine levels, inhibit inflammatory cell infiltration, and reduce demyelination in the spinal cord. Moreover, SHED-CM effectively inhibited the proliferation of myelin oligodendrocyte glycoprotein-specific $CD4^+$ T cells, which played a crucial role in the progression of autoimmune encephalomyelitis disease [7].

4. Effect of SHED-Derived Secretome on Angiogenesis

Angiogenesis plays a pivotal role in facilitating tissue regeneration. Research on the angiogenesis capacity of SHED-derived secretome has been conducted in various pathological conditions. Sugimura-Wakayama et al. (2015) demonstrated the capability of SHED-CM to promote tube formation in HUVECs and induce the expression of angiogenic factor VEGF in Schwann cells in vitro [8]. Similarly, de Cara et al. (2019) demonstrated the angiogenic effects of SHED-CM in HUVECs [9]. The study also revealed that 30-day treatment with SHED-CM

resulted in the successful induction of vascularised connective tissue within the root canal in a rat orthotopic model of dental pulp regeneration.

Kato et al. (2020) revealed that SHED-CM not only promoted tube formation in HUVECs but also accelerated HUVECs migration in wound healing and Boyden chamber assays [10]. SHED-CM was also able to promote ex vivo neovascularisation, as evidenced by the formation of neovessel sprouting from the aortic rings of Sprague Dawley rats. The in vivo study by Hiraki et al. (2020) also proposed cytokines and growth factors in SHED-derived secretome, particularly M-CSF, ANG, VEGF-A, MCP-1, VEGF-C, and bFGF, to be the main actors in the angiogenesis in the calvarial bone defect model of a mouse [11]. Additionally, VEGF, together with HGF, were also found to play roles in angiogenesis stimulation in the pressure ulcer mouse model [12].

5. Effect of SHED-Derived Secretome on Osteogenesis and Chondrogenesis

Previous studies reported that secretome derived from SHED plays important roles in promoting osteogenesis and chondrogenesis. Hiraki et al. (2019) reported that SHED-CM enhanced bone regeneration in a mouse model of the calvarial bone defect model [11]. This was evidenced by the increased formation of mature bone, increased abundance of collagen fibres and osteiods, and was notably superior to untreated mice. The study further revealed that SHED-CM contained a rich concentration of bone-metabolism-related markers, including OPG, OPN, BMP-2, and BMP-4, which likely contributed to bone regeneration.

Muhammad et al. (2020) investigated the regenerative effect of SHED-CM on osteoarthritis chondrocytes (OA) in vitro [13]. Interestingly, SHED-CM was first cultured in a serum-free medium for 48 or 72 h before being subjected to the interleukin-1β-stimulated chondrocytes for 24, 48, and 72 h. The growth factors in SHED-CM, such as TGF-β1, IL-10, and IL-6, were involved in chondrocyte growth, viability, proliferation, and protection. The treatment with SHED-CM not only improved the cell viability but also increased the expression of major markers of extracellular articular cartilage, aggrecan, and collagen type 2 (COL 2) in OA chondrocytes. Additionally, SHED-CM exhibited a modulatory effect on OA-induced inflammation by downregulating the levels of MMP-13 and NF-κB in OA chondrocytes. The findings were consistent with another study conducted by Giannasi et al. (2020), which also demonstrated the positive effects of the secretome derived from adipose-derived stem cells (ASCs) in protecting human articular chondrocytes (CH) from OA damage. The study revealed that the ASC-derived secretome reduced MMP activity and the expression of proinflammatory mediators associated with OA [14]. These consistent findings provide additional support for the potential therapeutic benefits of utilizing the secretome as an effective strategy to alleviate OA-induced inflammation and injury.

Vu et al. (2020) reported that SHED-CM treatment significantly restored the odontoblast/osteogenic differentiation of hydrogen peroxide (H_2O_2)-induced DPSCs, contributed by the effect of TGF-β, MMP, VEGF, FGF, Ils, and BMP in SHED-CM [15]. This was evidenced by the increased levels of odontoblast/osteogenic-related markers and enhanced mineral deposition in DPSCs, following treatment with SHED-CM. The study also suggested that these biological activities may be related to SMAD protein phosphorylation and MAPK signalling pathway.

6. Effect of SHED-Derived Secretome on Neuroprotection and Neuroregeneration

A growing body of literature has evaluated the neuroprotection and neuroregenerative effects of SHED-derived secretome in vitro and in vivo. Sugimura-Wakayama et al. (2015) reported various cytokines and growth factors such as NT-3, NGF, CNTF, HGF, GDNF, BDNF, and VEGF in SHED-derived secretome played an additive or synergistic role in peripheral nerve regeneration and in stimulating neuritogenesis, angiogenesis, and migration of Schwann cells, as well as in neurite outgrowth in dorsal root ganglion (DRG) neurons. The regeneration and recovery of nerves and axons were also observed in the in vivo study of the rat sciatic nerve model [8].

The SHED-derived secretome also showed benefits in treating neurodegenerative diseases. In a mouse model of perinatal HI-induced brain injury, treatment with SHED-CM led to a notable improvement in survival rate and neurological functions [1]. A study of permanent middle cerebral artery occlusion (pMCAO) in rats showed that SHED-CM promoted the migration and differentiation of endogenous neuronal progenitor cells (NPCs), reduced infarct volume, stimulated vasculogenesis, and subsequently improved motor function recovery [16].

In the assessment of Alzheimer's disease (AD) mouse models, Mita et al. (2015) showed that SHED-CM improved cognitive function and attenuated Aβ-induced inflammation, thus protecting the neurons against Aβ toxicity [17]. The study also found that SHED-CM suppressed glutamate-induced neuronal death in primary cerebral neurons derived from mouse embryos.

In the evaluation of the neurogenic potential of SHED-derived secretome for the treatment of Parkinson's disease (PD), Fujii et al. (2015) reported that CM obtained from both SHED and dopaminergic neuron-like SHED (dSHED) were able to protect the neurons against 6-OHDA toxicity and promoted neurite outgrowth in vitro [18]. Chen et al. (2020) found that SHED-CM improved motor deficits in the rotenone-induced PD rat model, marked by increased expression of tyrosine hydroxylase (TH) in the striatum and decreased in α-synuclein levels in nigra and striatum regions. Moreover, SHED-CM treatment significantly attenuated neuroinflammation in the brain of rotenone-induced PD rats by decreasing the Iba-1 and CD4 levels in the striatum, nigra, and cortex regions [19].

Taken together, these findings revealed the generative properties of SHED-derived secretome and its potential for the treatment of various pathological conditions. **Table 1** summarises the potential of the secretome of SHED in tissue regeneration, as reported in previous studies.

Table 1. Previous studies on the secretome derived from SHED.

Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
In vitro (SHED vs DPSCs)	To compare cytokine profiles produced by SHED and DPSCs.	IL-6, CNTF, CCL23, IGFBP2, IL-7, EGF, BMP6, IGFBP1, GM-CSF, Eotaxin1, IL-5, IFN-gamma, PARC,	SHED-derived secretome expressed more cytokines involved in odontogenesis, osteogenesis, and	[20]

Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
		IL-2, BLC, BDNF, MCP-1	immunomodulation, while DPSCs-derived secretome expressed more cytokines involved in angiogenesis.	
In vitro (DPSCs)	To investigate the potency of SHED-CM on DPSCs in pulp regeneration.	TGF-β, MMP, VEGF, FGF, Ils, BMP	SHED-CM showed a dose-dependent promotive effect on the proliferation, migration, and survival of DPSCs. Upregulation of marker genes for odontoblasts and osteogenesis and increased mineral deposition of impaired DPSCs in the presence of SHED-CM.	[15]
In vivo (Mouse calvarial bone defect model)	To investigate the effect of SHED-CM on bone regeneration.	TIMP-1, OPG, OPN, M-CSF, MCP-1, HGF, ANG, VEGF-C, IL-6, BDNF, NT-3, BMP-4, BMP-2, bNGF, FGF-2, GDNF, PDGF-BB, EGF	Bone regeneration was improved in the defects treated with stem cells and CM compared to controls 8 weeks after transplantation. Mature bone formation and angiogenesis were confirmed with SHED-CM but not with stem cells or in controls.	[11]
In vitro (OA chondrocytes)	To evaluate the regenerative effect of SHED-CM on OA chondrocytes for cartilage repair and regeneration.	TGF-β1, IL-10, IL-6	SHED-CM protected chondrocytes by increasing matrix proteins and suppressed MMP-13 expression. SHED-CM attenuated the inflammatory assault induced by IL-1β. The regenerative effect of SHED-CM could be attributed to secreted factors modulating catabolic processes towards an anabolic phenotype by downregulating NF-κB.	[13]
In vitro (HUVECs)	To examine the beneficial effects of	n/a	SHED-CM significantly increased the proliferation	[10]

Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
In vivo (Mouse Matrigel plug assays) Ex vivo (Rat aortic ring assay)	secreted factors from SHED on endothelial cells to promote angiogenesis.		of HUVECs. SHED-CM accelerated the migration of HUVECs in wound healing and Boyden chamber assays. SHED-CM induced complex tubular structures of HUVECs in a tube formation assay. SHED-CM significantly increased neovascularisation in rat aorta. The angiogenic effects of SHED-CM were equal to or greater than the effective concentration of VEGF.	
In vitro (HUVECs) In vivo (Rat model of orthotopic dental pulp regeneration)	To evaluate the effect of SHED-CM on the proliferation, differentiation, migration ability, cell death, gene expression, and production of VEGF.	n/a	SHED-CM significantly induced lower expression of 7AAD in HUVECs, whereas the expression of the Ki67 was similar in all groups. SHED-CM induced expression of VEGF-A. SHED-CM significantly induced higher VEGF synthesis than other media. SHED-CM induced the formation of vascularised connective tissue inside the root canal.	[9]
In vitro (Human breast cancer stem cells (BCSCs))	To evaluate the stemness and proliferation of human BCSCs after being supplemented with heated secretome from SHED.	n/a	The heated secretome of SHED contained activated TGF-β1, which increased the expression of stemness genes, OCT4, and ALDH1A1, as well as the proliferation of human BCSCs (ALDH+) via TGF-β1 paracrine signalling.	[21]
In vivo (Rat with ALF)	To study the multifaceted therapeutic benefit of	HGF, MMP-10, MCP-1, ANG, SCF, IGFBP-2, sIL-6R, EGFR, FSTN, MMP-	SHED-CM attenuated the ALF-induced inflammation by suppressing the proinflammatory cytokine	[4]

Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
	SHED-CM in ALF in rats.	3, spg130, GRO, MIP-1β, MIF, RAGE, TIMP-4, adipsin, OPG, CXCL16, IGFBP-1, BDNF, LAP, GDNF, sTNFR1, TGF-β2, FGF-7, MMP-13, MMP-9, Flt-3 L, Dkk-3, NID-1, VEGF-A, CTSS, HVEM, GDF-15, TIMP-1, B2M, EG-VEGF, β-IG-H3, TIMP-2, IL-6, MCP-3, PAI-1, uPAR, IGFBP-6, Dkk-1, MMP-1	levels (IL-6, TNFα, IL-1β, and iNOS), increasing the anti-inflammatory cytokine levels (IL-10 and TGF-β1), and M2 cell markers. SHED-CM promoted hepatocyte proliferation and inhibited apoptosis. SHED-CM induced angiogenesis.	
In vitro (Myelin oligodendrocyte glycoprotein-specific $CD4^+$ T cells) In vivo (A mouse model of multiple sclerosis (MS))	To investigate the efficacy of SHED-CM in treating experimental autoimmune encephalomyelitis, a mouse model of MS.	n/a	In vitro: SHED-CM inhibited the proliferation of myelin oligodendrocyte glycoprotein-specific $CD4^+$ T cells. In vivo: SHED-CM exhibited significantly improved disease scores, reduced demyelination, and axonal injury. SHED-CM reduced inflammatory cell infiltration and proinflammatory cytokine expression (IFN-γ, IL-17, and TNF-α) in the spinal cord.	[7]
In vitro (Schwann cells and DRG cells) In vivo (Rat model of sciatic nerve transection)	To investigate the effect of SHED-CM in the regeneration of the peripheral nerve.	NT-3, NGF, CNTF, HGF, GDNF, BDNF, VEGF	In vitro: SHED-CM significantly increased proliferation, migration, and the expression of neuron-, extracellular matrix (ECM)-, and angiogenesis-related genes in Schwann cells. SHED-CM stimulated the neuritogenesis of DRG cells and increased cell	[8]

Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
			viability. SHED-CM enhanced tube formation in an angiogenesis assay. In vivo: SHED-CM promoted axon regeneration and functional recovery. SHED-CM reduced muscle atrophy.	
In vitro (Cerebellar granule neurons (CGNs) isolated from newborn rats)	To evaluate the trophic actions of SHED-CM and dSHED-CM on neurite outgrowth and apoptosis in CGNs isolated from newborn rats.	n/a	SHED-CM or dSHED-CM significantly suppressed the 6-OHDA-induced apoptosis in CGNs isolated from newborn rats. Neurite outgrowth was significantly enhanced by SHED-CM and dSHED-CM.	[18]
In vitro (Glutamate-induced neurons from the cortices of C57BL/6 mice embryos) In vivo (A mouse model of Aβ-induced AD)	To investigate the therapeutic benefits of a serum-free SHED-CM in a mouse model of AD.	n/a	SHED-CM attenuated the proinflammatory (IL-1β, TNF-α, and iNOS) and induced anti-inflammatory M2-like microglia. SHED-CM improved cognitive function. SHED-CM inhibited oxidative-nitrosative stress (3-NT and iNOS) in the cerebral parenchyma. SHED-CM promoted the expression of multiple neurotrophic factors (BDNF, NGF, and IGF-1). SHED-CM suppressed glutamate-induced neuronal death.	[17]
In vivo (A mouse model of I/R)	To investigate the impact of SHED-CM on myocardial injury in a mouse model of I/R.	VEGF, IGF-1, HGF, bFGF, SDF-1, EGF, SCF	SHED-CM reduced the size of myocardial infarct, inhibited myocyte apoptosis, and suppressed inflammatory cytokine levels (IL-6, IL-1β, and TNFα).	[3]

Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
In vivo (A rat model of SCI)	To investigate the effect of SHED-CM in a rat model of SCI.	MCP-1, ED-Siglec-9	SHED-CM improved functional recovery after SCI. SHED-CM suppressed expressions of proinflammatory cytokines (IL-1β, TNF-α, and iNOS) and induced anti-inflammatory M2-like macrophages.	[5]
In vivo (A mouse model of streptozocin-induced diabetes)	To investigate the effect of factors secreted by SHED on β-cell function and survival.	n/a	SHED-CM suppressed inflammatory chronic response of macrophage. SHED-CM promoted lung regeneration. SHED-CM increased insulin secretion, β-cell proliferation, and reduced apoptosis.	[2]
In vivo (A mouse model of BLM-induced ALI)	To investigate the effects of SHED-CM in a mouse model of BLM-induced ALI.	n/a	SHED-CM attenuated lung injury and weight loss in BLM-treated mice and improved their survival rate. SHED-CM attenuated the BLM-induced proinflammatory response and promoted the induction of anti-inflammatory M2-like lung macrophage. SHED-CM suppressed the BLM-induced tissue damage and inhibited the expression of α-SMA. SHED-CM promoted the M2 differentiation of bone marrow-derived macrophages in vitro.	[6]
In vivo (Rat model of pMCAO)	To investigate the effects of SHED-CM in a rat model of pMCAO.	n/a	SHED-CM improved motor function recovery. SHED-CM increased the expression of doublecortin (DCX), neurofilament, neuronal nuclei, and rat endothelial cell antigen in the peri-infarct area.	[16]

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Type of Study	Purpose	Secreted Soluble Factors	Key Findings	References
			SHED-CM induced the migration of NPCs from the subventricular zone to the peri-infarct area.	
In vivo (A mouse model of perinatal HI-induced brain injury)	To investigate the effects of SHED-CM for the treatment of neonatal HI brain injury.	n/a	SHED-CM exhibited significant reductions in apoptosis and tissue loss. SHED-CM improved neurological functions.	[1]

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The properties of SHED-derived secretome make it an attractive tool for use in regenerative medicine. Its immunomodulatory effects, its ability to promote tissue regeneration and angiogenesis, and its lower risk of tumour formation and immune rejection make it a promising alternative to live cell therapy. However, further research is needed to understand the mechanisms underlying these properties fully and to optimise their production and use. With further research and development, the secretome of SHED has the potential to become a valuable tool in the field of regenerative medicine.

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