The Therapeutic Potential of Secreted Factors from Dental Pulp Stem Cells for Various Diseases

Kenichi Ogata *, Masafumi Moriyama, Mayu Matsumura-Kawashima, Tatsuya Kawado, Aiko Yano and Seiji Nakamura

Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; moriyama@dent.kyushu-u.ac.jp (M.M.); mayu8mayu@dent.kyushu-u.ac.jp (M.M.-K.); t.kawado@dent.kyushu-u.ac.jp (T.K.); a.yano@dent.kyushu-u.ac.jp (A.Y.); seiji@dent.kyushu-u.ac.jp (S.N.)

* Correspondence: k.ogata@dent.kyushu-u.ac.jp; Fax: +81-92-642-6386

Abstract: An alternative source of mesenchymal stem cells has recently been discovered: dental pulp stem cells (DPSCs), including deciduous teeth, which can thus comprise potential tools for regenerative medicine. DPSCs derive from the neural crest and are normally implicated in dentin homeostasis. The clinical application of mesenchymal stem cells (MSCs) involving DPSCs contains various limitations, such as high cost, low safety, and cell handling issues, as well as invasive sample collection procedures. Although MSCs implantation offers favorable outcomes on specific diseases, implanted MSCs cannot survive for a long period. It is thus considered that their mediated mechanism of action involves paracrine effects. It has been recently reported that secreted molecules in DPSCs-conditioned media (DPSC-CM) contain various trophic factors and cytokines and that DPSC-CM are effective in models of various diseases. In the current study, we focus on the characteristics of DPSC-CM and their therapeutic potential against various disorders.

Keywords: dental pulp stem cells; secreted factors; anti-inflammatory; immunosuppression; M2-type macrophages

1. Background

The oral environment, which consists of teeth, gums, and the tongue, is one of the most specialized formations of the craniofacial skeleton and forms an excellent developmental model of organ formation. In addition, this complex and sophisticated structure offers great potential for regenerative medicine due to the abundant resources of highly specialized mesenchymal stem cells (MSCs). The most recently discovered stem cells in the mesenchymal stem cell repertoire, dental stem cells, appear to have immense potential for developmental, differentiation, regeneration, and immunomodulatory properties.

The discovery of dental stem cells has made great strides toward research and clinical application, highlighting the importance of this interesting source of stem cells.

Dental pulp stem cells (DPSCs) deriving from child or adult human dental pulp were initially discovered by Gronthos and colleagues in 2000 [1], although the presence of stem cells in dental pulp has been previously reported by Yamamura in 1985 [2]. DPSCs were isolated on the basis of high proliferation and colonization frequency, producing sporadic but densely calcified nodules. In addition, DPSCs do not significantly differ from MSCs deriving from adipose tissue, bone marrow, and umbilical cord tissue with respect to their internationally accepted vague criterion of plastic adherence and their ability to differentiate into osteoblasts, chondrocytes, and adipocytes in vitro while expressing mesenchymal (CD29, CD90, CD105, CD73, and CD44) but not hematopoietic lineage markers (CD14, CD34, and CD45) [3]. It was suggested by the Committee of Mesenchymal Stem Cells and Tissues of the International Society for Cellular Therapy in 2005 that 95% of
human MSCs expresses at least the following surface antigens, CD105 (endoglin), CD73 (5′-ectonucleotidase), and CD90/Thy-1 (glycosylphosphatidylinositol-anchored glycoprotein); however, they do not express (less than 2%) the surface antigens CD11b, CD14, CD19, CD34, CD45, CD79a, and HLA-DR. Nevertheless, other studies have reported different cell surface antigens in the prospective isolation of MSCs, such as STRO-1 (stromal precursor antigen 1), VCAM-1 (vascular cell adhesion molecule 1), SH2 (Src homology 2), SH3/SH4, CD271, CD2, and SSEA4 (stage-specific embryonic antigen-4) [4–8]. Thus, there are various differences in the expression of surface markers of DPSCs depending on the reports.

MSCs are known to be involved in growth, wound healing, and cell replacement under both normal and disease states. These cells have demonstrated effectiveness in regenerating periodontal tissue, diabetic critical limb ischemic tissue, bone damage triggered by osteonecrosis, skin lesions after burns [9–11], as well as liver, neuronal and skeletal muscle tissues, and blood vessels [12–15] among other tissues [16]. To date, there have been many preclinical experiments using DPSCs, and there are reports that DPSCs are differentiated into various cells, e.g., neural cells, dopaminergic neurons, myotubes, hepatocyte-like cells, and keratocytes [17–21]. However, there are no reports on large-scale clinical trials. The problem with using stem cells is the risk of cancer and the necessity for special cell processing facilities.

Various previous studies have demonstrated that transplanted cells can have multiple and significant roles; they not only can travel in their host tissues and participate directly in tissue regeneration [22], they can also present paracrine effects [23–27]. DPSCs produce cytokines that can reduce inflammation, increase progenitor cell proliferation, ameliorate tissue repair, and reduce infection more effectively compared to bone marrow-derived MSCs (BMMSCs) [28]. The goal of this review is thus to highlight the therapeutic effect of secreted factors from DPSCs for various diseases as well as their mechanism of action.

2. Cytokines Contained in DPSC-CM

As presented in Table 1, previous reports have shown that DPSC-conditioned media (DPSC-CM) contain more anti-inflammatory cytokines than BMMSC-conditioned media (BMMSC-CM) [29–31], e.g., interleukin (IL)-10, 34 times higher; IL-13, 63 times higher; follistatin, 15 times higher; transforming growth factor (TGF)-β1, 7 times higher (Table 1). Moreover, hepatocyte growth factor (HGF), neural cell adhesion molecule-1 (NCAM-1), adiponectin, ectodomain of sialic acid-binding Ig-like lectin-9 (ED-Siglec-9), matrix metalloproteinase (MMP)-13, neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and MMP-9 were detected only in DPSC-CM. Based on the above, DPSC-CM contain a higher number of anti-inflammatory cytokines compared to BMMSC-CM.

Table 1. The anti-inflammatory factors or DPSC-CM only detected factors of DPSC-CM vs. BMMSC-CM.

| Anti-Inflammatory Factors | BMMSC-CM | DPSC-CM |
|--------------------------|----------|---------|
| Follistatin              | 2328     | 36241   |
| TGF-β1                   | 2186     | 11623   |
| IL-10                    | 234      | 7989    |
| IL-13                    | 80       | 5098    |
| VEGF                     | 1242     | 3549    |
| IGF-1                    | 3324     | 3521    |
| HGF                      | 0        | 1857    |
| TECK                     | 1513     | 1609    |
| MCP-1                    | 483      | 965     |
| IL-29                    | 1019     | 943     |
| Adiponectin              | 0        | 502     |
| ED-Siglec-9              | 0        | 396     |
| GM-CSF                   | 188      | 159     |
Table 1. Cont.

| Secreted Factors Only in DPSC-CM (Intensity) |
|---------------------------------------------|
|                                             |
| BMMSC-CM                                    |
| DPSC-CM                                     |
| HGF 0                                       | 1857 |
| NCAM-1 0                                    | 573  |
| Adiponectin 0                               | 502  |
| ED-Siglec-9 0                              | 396  |
| MMP-13 0                                    | 377  |
| NT-3 0                                      | 249  |
| BDNF 0                                      | 179  |
| MMP-9 0                                     | 136  |

Abbreviations: TGF-β1: transforming growth factor-β1; IL-10: interleukin-10; IL-13: interleukin-13; VEGF: vascular endothelial growth factor; IGF-1: insulin-like growth factor-1; HGF: hepatocyte growth factor; TECK: thymus-expressed chemokine; MCP-1: monocyte chemoattractant protein-1; IL-29: interleukin-29; ED-Siglec-9: ectodomain of sialic acid-binding immunoglobulin-type lectin-9; GM-CSF: granulocyte macrophage colony-stimulating factor; NT-3: neurotrophin-3; BDNF: brain-derived neurotrophic factor.

3. Cerebrovascular Disease

There are some studies regarding conditioned media therapy of the central nervous system (CNS) [32–35]. Engraftment of DPSCs promotes the functional recovery from various acute and chronic CNS insults through paracrine mechanisms that induce endogenous tissue-repairing activities [36–39]. The mechanisms of DPSC-CM for CNS are summarized below.

Stroke is the third leading cause of death globally and the most common cause of long-term disability in humans [40]. Lately, transplantation of bone marrow mononuclear cells was revealed to accomplish clinical efficacy by promoting angiogenesis in patients with cerebral ischemia [40,41]. In a focal cerebral ischemia animal model, DPSC-CM and BMMSC-CM equally inhibited the expression of pro-inflammatory cytokines and markers of oxidative–nitrosative stress [32]. Conversely, DPSC-CM activated M2-type microglia selectively, leading to the expression of the mRNA-encoding BDNF, a neurotrophin that has a key role in the synaptic remodeling correlated with memory development in the adult hippocampus [32]. In an aneurysmal subarachnoid hemorrhage (aSAH) rat model, a potential synergistic effect from DPSC-CM was observed. In particular, high levels of tissue inhibitor of metalloproteinases (TIMP)-2 in DPSC-CM were observed, which are crucial for the maintenance of tissue homeostasis [35]. TIMP-2 is an inhibitor of MMP-3 and -9 and has been shown to be significantly associated with an increased risk of soft tissue trauma, such as Achilles tendinopathy [42]. With respect to the functional study of TIMP-2 in the neural system, it was considered to be substantially valuable for noise-related cochlear injury [43].

4. Heart Disease

Ischemic heart diseases, as for instance myocardial infarction (MI), are among the leading causes of death worldwide [44]. MI usually results in irreversible damage in heart tissues, and the associated mortality and morbidity remain high [45]. The development of effective adjunctive therapies for patients with MI is thus still essential.

Administration of DPSC-CM reduced MI and enhanced cardiac function in mice after ischemia reperfusion (I/R). This correlated with ischemic heart apoptosis and reduced inflammation [46,47]. Yamaguchi S et al. showed that DPSC-CM induced cardiomyocyte survival in response to hypoxia and serum deprivation, and that DPSC-CM reduced the expression of pro-inflammatory mediators promoted by lipopolysaccharide (LPS) [46]. DPSC-CM administration can thus protect the heart from ischemic damage by at least two mechanisms mediating reduction of cardiomyocyte death and suppression of inflammatory responses in myocardial cells.
5. Lung Disease

Acute respiratory distress syndrome (ARDS) is a devastating inflammatory disease characterized by diffuse pulmonary injury and consequent fibrosis, leading to respiratory failure and death [48,49]. ARDS development takes place in two phases; the exudative phase is characterized by loss of alveolar structure and accumulation of inflammatory cells at the site of injury. The shift from the exudative phase to the proliferative phase is characterized by fibroblast proliferation and differentiation in myofibroblasts and excessive extracellular matrix deposition. Once remodeling was confirmed, the fibrosis evolves to an irreversible state that further accelerates pulmonary dysfunction and raises mortality rates. The development of efficient treatments focused on reversing or suppressing ARDS progression is currently studied. The pro-inflammatory M1 and anti-inflammatory M2-type macrophages are considered to represent the extreme activation states of macrophage activation [50–52].

In mouse bleomycin (BLM)-induced acute lung injury (ALI), administration of DPSC-CM enhanced BLM-induced lung fibrosis, at least partially, via the conversion of a pro-inflammatory M1 environment to an anti-inflammatory M2 [53]. In contrast, BMMSC-CM relatively reduced the BLM-induced pro-inflammatory response but did not promote M2 cell differentiation or enhancement of pulmonary fibrosis. These results can be in contrast to these in a previous study in which the administration of mouse BMSC-CM was shown to promote M2 macrophage differentiation in the injured lungs of lipopolysaccharide-treated mice [54]. Moreover, DPSC-CM stimulated the in vitro differentiation of mouse bone marrow-derived macrophages into M2 macrophages expressing Arginase 1, CD206 and Ym-1 in an in vitro study. Thus, treatment with DPSC-CM induces an anti-inflammatory M2 environment and significantly ameliorates the injured lung’s state.

6. Liver Disease

Acute liver failure (ALF), which can be caused by various parameters such as drugs, viruses, and ischemiatoxins, can lead to massive hepatocyte destruction and an unlimited inflammatory response [55]. Although the liver has inherent tissue-repairing activities that induce the division of mature hepatocytes and the proliferation or differentiation of adult liver stem/progenitor cells (LPCs) [56], when acute tissue loss overcomes the liver’s regenerative capacity, the impaired hepatic function results in systemic inflammation, multiple organ failure and sudden death [57]. When ALF becomes chronic, it evolves to liver fibrosis (LF), which is a result of many chronic liver diseases, such as viral infection and autoimmune hepatitis, alcohol abuse, and the use of specific drugs [58].

In rat ALF models, BMMSC-CM was revealed to present therapeutic benefits [59,60]. Nevertheless, which effect was limited. Matsushita Y et al. and Hirata M et al. recommended that DPSC-CM comprised various efficient factors for ALF treatment [61,62]. HGF is a multifunctional protein that prevents hepatocyte apoptosis and induces the proliferation of LPCs and neovascularization [63,64]. Stem cell factors (SCF) inhibit hepatic apoptosis in acetaminophen-induced ALF and is involved in the induction of LPCs [59,65]. Insulin-like growth factor-binding protein (IGFBP)-1 and TIMP-1 inhibit hepatocyte apoptosis in ALF promoted by various stimuli [66,67]. Angiogenin, vascular endothelial growth factor (VEGF)-A and endocrine-derived vascular endothelial growth factor (EGVEGF) are established angiogenic promoters that play key roles in neo-vascularization after liver injury [68–70]. In addition, MCP-1 and IL-6 induce survival of human CD11b+ peripheral blood mononuclear cells and M2-type macrophage polarization [71]. Favorable factors included within the DPSC-CM and endogenous tissue-repairing factors induced by DPSC-CM therapeutic function in combination attenuate D-galactosamine-induced ALF or carbon tetrachloride-induced LF.
7. Eye Disease

Retinitis pigmentosa (RP) is a hereditary disorder associated with photoreceptor degeneration and loss. Its inheritance can be autosomal dominant, autosomal recessive, or X-linked. RP has varying incidence in different ethnic groups, and it affects globally 1 in 4000 people, concerning a total of over 1 million individuals [72]. Some RP patients become blind with aging; approximately 25% become officially blind (20/200), and 0.5% become completely blind in both eyes [73]. The discovery of an effective and safe treatment for retinal degenerative diseases would significantly help patients and support reduction of the economic burden on society.

Li XX et al. showed that subretinal injection enables DPSCs or DPSC-CM to contact the photoreceptors directly [74]. It was demonstrated that DPSC-CM resulted in a similar therapeutic effect as DPSCs [74,75]. Although the main effect is believed to be its anti-apoptotic activity, the pathway to the effects of DPSC-CM, which lasts for several months, remains unclear by further studies of eye disease.

8. Neurological Disorder

Spinal cord injury (SCI) is commonly caused by an accident or a fall, developing in a disorder in motor or sensory function [76]. When the spinal cord is injured, late effects such as paralysis of the limbs may persist, which may result in severe difficulties in daily life. The development of SCI is significantly associated with the development of inflammation at the site of injury. There are two types of macrophages, M1 and M2. M1 macrophages digest debris and are involved in inflammation, while M2 macrophages act to reduce inflammation. M1 macrophages promote inflammation by secreting pro-inflammatory cytokines and nitric oxide. M1 macrophages also play an important role in the recruitment and activation of astrocytes. Conversely, M2 macrophages induce tissue repair by releasing anti-inflammatory cytokines [77–80]. Transplantation of DPSCs in a mouse model after SCI presented in previous studies was found to secrete various trophic factors, such as BDNF and GDNF, and significantly enhanced motor function [81,82]. Furthermore, released ED-Siglec-9 and monocyte chemoattractant protein-1 (MCP-1), which are found specifically in DPSC-CM, induced significant functional recovery in a rodent SCI model by promoting an M2-dominant neuro-repairing microenvironment [83]. Additionally, Kano F et al. demonstrated that MCP-1 and ED-Siglec-9 are crucial for DPSC-CM-mediated functional recovery after facial nerve injury (FNI) in a rat model [84]. Importantly, MCP-1/sSiglec-9 promoted polarization of M2 macrophages, which competed the pro-inflammatory M1 conditions correlated with FNI, induced proliferation, migration, and differentiation of Schwann cells, and increased neurite extension of peripheral nerves.

Parkinson’s disease (PD), the second most common neurodegenerative disease, is characterized by gradual loss of dopaminergic neurons in the substantia nigra [85,86]. In a PD animal model, DPSC-CM-mediated mechanisms may involve C α-synuclein accumulation and reduced levels of CD4-positive cells [87].

Alzheimer’s disease (AD) is a developing neurodegenerative disease, characterized by deterioration of cognitive function linked with the deposition of β-amyloid (Aβ) peptides in the brain [88–91]. Nevertheless, the exact pathways involved in Aβ-induced neurotoxicity and neuroinflammation are not currently understood. In an AD-like mouse model, DPSC-CM inhibited 6-hydroxydopamine-induced cell death and promoted the neurite growth of cerebellar granule neurons [92], as DPSC-CM comprised various types of neuroprotective factors including BDNF, HGF, MMP-9, and TGF-β. In particular, DPSC-CM promoted specifically M2-type microglia, leading to expression of the mRNA encoding BDNF, a neurotrophin playing a key role in the synaptic remodeling correlates with memory formation in the adult hippocampus. The multidimensional activities of DPSC-CM may support many neuro-reparative effects required for the therapy of cognitive deficits.

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that causes destruction of upper and lower motor neurons in the CNS [93]. After diagnosis, the disease typically progresses to advanced stages, and there are limited therapeutics and no cure for
ALS mainly because of the disease presentation characteristics. Using an ALS mouse model, Wang J et al. assessed the therapeutic effect of DPSC-CM systemic administration [94]. However, the mechanism involved in DPSC-CM’s therapeutic benefit remains unclear. In early disease, systemic DPSC-CM administration can directly cause a therapeutic benefit to spinal neurons or cells involved in neuromuscular junctions, including Schwann and muscle cells. As demonstrated in Table 1, DPSCs secrete various potent neurotrophic factors, such as NGF, BDNF, VEGF, and NT, which have established therapeutic benefits for SCI and other neurodegenerative diseases [35,36,82,95]. These factors could thus directly protect motor neurons, leading to increased survival.

Multiple sclerosis (MS) is a demyelinating disease of the CNS. MS predominantly affects young adults, with an onset average age of approximately 30 years. The origin of MS is not yet clear, but it is considered to develop from immune defects. The main symptoms involve impaired vision, nystagmus, and swallowing and talking difficulties. The protective effect of DPSC-CM has been demonstrated in the treatment of experimental autoimmune encephalomyelitis (EAE), which is one of the MS models. Administration of DPSC-CM decreased expression of inflammatory cytokines in the spinal cord, inhibited demyelination, and enhanced EAE clinical scores [96]. Shimojima C et al. reported that despite the effect of DPSC-CM on EAE depending on ED-Siglec-9, DPSC-CM–treated mice demonstrated relatively improved recovery compared to ED-Siglec-9–treated mice, indicating that other factor(s) in DPSC-CM, including HGF, could cooperatively improve EAE [96].

9. Autoimmune Disease

As MSCs are exceptional as immunosuppressive agent candidates during solid-organ transplantation and for treating graft vs. host disease, inflammatory diseases, as well as other autoimmune diseases [97,98]. Early studies have demonstrated that DPSCs block the proliferation of stimulated T cells, with a more robust pattern compared to BMMSCs [99,100]. DPSCs inhibited peripheral blood mononuclear cells (PBMCs) proliferation that was stimulated with mitogen or was in an allogeneic-mixed lymphocyte reaction, suggesting that the immunosuppressive properties of MSC-like cells are expected to include soluble factors mediated by signaling molecules derived from activated PBMCs [101]. In previous studies, it has been demonstrated that toll-like receptors are generally distributed in cells of the immune system and can activate immunosuppression of the DPSCs via improving the expression of TGF-β and IL-6 [102,103].

Most recently, Matsumura-Kawashima M et al. administrated DPSC-CM in non-obese diabetic (NOD) mice as primary Sjögren’s syndrome (SS), which is a chronic, systemic autoimmune condition characterized by inflammation of exocrine glands and functional impairment of the salivary and lacrimal glands [30]. DPSC-CM developed a protective effect on the secretory function of salivary glands (SMGs). Furthermore, DPSC-CM developed hyposalivation caused from SS by reducing inflammatory cytokine expression, promoting regulatory T cells (Treg) in the spleen via the TGF-β/Smad pathway, controlling the local inflammatory microenvironment, and reducing apoptosis in SMGs. Accordingly, Ogata K et al. discovered that DPSC-CM alleviated hyposalivation caused by SS in MRL/MpJ-faspr/faspr mice, which can take place in accordance with other rheumatic diseases (secondary SS) models, by reducing the number of inflammatory cytokines, controlling the local inflammatory microenvironment, and reducing apoptosis in SMGs [31].

10. Bone and Cartilage Disease

Articular cartilage (AC) plays vital roles in the operation of diarthrodial (synovial) joints [104,105]. Cartilage injuries are relatively common, mainly in young and active athletes, especially in the knee joint [106–108]. They are often thought as risk factors for the development of osteoarthritis (OA) in later life, a degenerative and inflammatory disease of the synovial joint with irreversible cartilage loss [104]. OA causes disability, especially in the elderly, and correlates with a large socio-economic burden [109,110].
Matrix-induced autologous chondrocyte implantation (MACI) has been developed aiming to restore damaged cartilage tissue [111]. Nevertheless, MACI contains several limitations such as potential iatrogenic damage and high associated costs [112–114]. To overcome these limitations, the use of innovative autologous tissue engineering approaches using stem cells has created an increasingly interesting area aimed at achieving AC regeneration.

DPSC-CM can promote endogenous cells to proliferate and replace the lost tissue, while it can inhibit progression of cartilage loss by impairing chondrocyte apoptosis [115]. Furthermore, Lo Monaco M et al. suggested that DPSC-CM might cause multiple anti-inflammatory and anti-catabolic effects in OA chondrocytes [115]. Elucidation of the paracrine effects of DPSCs and improved understanding of stem cell regulation provide researchers with a significant number of trauma treatment options that have been limited by cell procurement concerns.

The temporomandibular joint (TMJ) is a load-bearing articulator with various motions comprising rotation and translation [116]. The AC in a typical synovial joint is a thin layer of hyaline cartilage that covers the entire articular surface of each bone. TMJ osteoarthritis (TMJOA) is a degenerative joint disease, characterized by progressive cartilage degeneration, abnormal bone remodeling, and chronic pain [117]. The mechanisms causing TMJOA are complex and multidimensional. Nevertheless, it has been indicated that increased malocclusion causes mechanical stress impacts during TMJOA development [118]. In the advanced stage, the tissue-degenerated TMJOA microenvironment induces cartilage matrix degradation, chondrocyte apoptosis, and necrosis; In addition, irregular resorption of subchondral bone causes irreversible joint damage and dysfunction [119,120]. Ogasawara N et al. employed a mechanical-stress-associated TMJOA model comprising five consecutive days of TMJ damage followed by treatment with DPSC-CM for the following five days after TMJ damage [121]. DPSC-CM comprised various therapeutic factors with the ability of TMJOA treatment. DPSC-CM not only prevented the articular degradation cascade but also regenerated the injured articular joint by inducing proliferation of the multipotent polymorphic cell layer and development of the cartilage matrix in mice with TMJOA. Furthermore, they discovered several exosome markers such as Alix, tumor susceptibility 101 (TSG101), integrin α chains, and tetraspanin (TSPANs, CD9, CD63, CD81) that are representative members of a protein superfamily characterized by the occurrence of four transmembrane and two extracellular domains. This indicates that DPSCs may secrete a higher number of exosomes compared to what was previously considered [121,122]. Nevertheless, in order to elucidate the exact mechanisms of DPSC-CM-mediated AC regeneration, the evaluation of therapeutic factor accessibility in DPSC-CM toward injured TMJ is essential.

Bisphosphonate (BP) therapeutics are valuable in osteoporosis treatment, Paget disease of bone, bone metastasis from malignant tumors, multiple myeloma, and hypercalcemia, as well as in inhibiting and improving a range of bone-associated conditions [123,124]. Nevertheless, BP preparations tend to promote osteoclast (OC) apoptosis and inhibit angiogenesis [125,126]. Despite the fact that drug-related osteonecrosis of the jaw (MRONJ) has been described as a symptom associated with BP preparations, no effective treatment has yet been discovered. Several therapeutic approaches have been suggested to date aiming to increase conservative and non-invasive modalities [127,128], but these methods provide a limited delay on symptom progression and fail to accomplish complete remission. Various reports involved DPSC-CM administration on a MRONJ rat model generated using sodium zoledronate (ZOL) administration, and after performing dental extraction, they evaluated the effects of DPSC-CM on OC and osteoblasts (OB), and assessed osteonecrosis and angiogenesis improvement [129,130]. DPSC-CM comprises angiogenic growth factors, such as VEGF (Table 1) and IL-8 [131]. These factors may promote epithelial tissue formation by increasing vascular endothelial cell numbers and by inducing chemotaxis [131], thus improving bone exposure. DPSC-CM were also found to express MCP-1 (Table 1). Based on previous reports, OC precursors result from monocytes. MCP-1 is a monocytic, chemotactic protein that induces monocyte and lymphocyte chemotaxis and increases IL-1 and IL-6
secretion [132,133]. The protein may promote OC synthesis by increasing the accumulation and induction of OC precursors.

11. Metabolic Disease

Diabetes mellitus is a metabolic condition characterized predominantly by chronic hyperglycemia, which is caused from insulin resistance or from impairment of insulin secretion. In total, 75% of obese patients do not develop diabetes due to the effect of compensatory insulin secretion; maintenance of functional pancreatic β-cells is thought to be the ultimate result of diabetes treatment [134]. Existing antidiabetic drugs are inadequate to reduce progressive damage in pancreatic β-cells. As a result, patients need to eventually switch to insulin therapy [135]. Islet transplantation and regenerative medicine thus continue to receive increased interest as a developing treatment option for diabetes [136]. Moreover, diabetic polyneuropathy (DNP), the most common diabetic complication in both type 1 and type 2 diabetes, impacts up to 50% of these patients [137]. Symptoms of DPN include spontaneous pain, hyperalgesia, and diminished sensation [138]. Pathogenesis of DPN involves degeneration of nerve fibers and decreased nerve blood flow. Tight glycemic control is essential for the reduction of DPN progression but not its complete inhibition [139]. Additionally, multifactorial intervention targeting hyperglycemia, hypertension, and dyslipidemia failed to decrease the risk of DPN in patients with type 2 diabetes [140]. Although symptomatic therapy drugs for painful DPN are useful for amelioration of patients’ quality of life, essential therapies for the pathogenesis of DPN are still necessary.

DPSC-CM regenerated pancreatic β-cells in streptozotocin (STZ)-stimulated diabetic mice, in which pancreatic β-cells were substantially destroyed in this mouse. Izumoto-Akita T et al. recommended that factors secreted from stem cells (paracrine signals) could be responsible for this process [141]. Previous studies have demonstrated that VEGF plays a crucial role in the proliferation and development of pancreatic β-cells [142], and stimulation of phosphoinositide 3-kinase suppresses cell death, proliferation, and pancreatic β-cells function [143]. Moreover, examination of fractionated DPSC-CM based on molecular weight revealed that compared to DMEM, a fraction of more than 100 kDa enhanced viability of STZ-treated MIN6 cells (mouse pancreatic β-cell line) [141]. DPSCs have been described to differentiate into pancreatic β-like cells [144], indicating that DPSC-CM commonly comprise secreted factors affecting differentiation pathways, function, and secretion among neural cells and pancreatic β-cells. Based on the above, DPSC-CM therapy was more efficient in stimulating growth and insulin secretion in pancreatic β-cells compared to BMMSC-CM therapy.

With respect to DNP, the combination of angiogenesis, neuronutrition, and immunomodulatory results could indicate multiple improvements in diabetic polyneuropathy. VEGF gene transfer to the lower limbs enhanced vascularity as well as the symptoms of diabetic polyneuropathy [145,146]. Based on that, the therapeutic mechanisms of DPSC-CM on DNP are the following: (1) angiogenesis and blood flow improvement, (2) anti-inflammatory effect, and (3) neuroprotective effect [147–149].

12. Dental Diseases

Dental trauma, restorative operative procedures, and/or caries lesions may expose the dental pulp [150]. Coping with this clinical condition in dentistry is challenging, as maintenance of the dentin–pulp complex vitality is crucial. When the exposure of dental pulp takes place in immature teeth with no complete root formation, this problem is even worst since the rhizogenesis procedure is disrupted [151].

Achieving ischemia or necrosis during enhanced tissue cell-based regeneration depends on functional re/angiogenesis and functional survival of transplanted cells [152]. The ability of these cells to regenerate is based on their proliferation, integration, and differentiation characteristics, and on the potential of secretory proteins, such as trophic factors, growth factors, cytokines, and chemokines, which positively affect damaged tissue [153].
These secreted factors, when used without the stem cells, can trigger tissue repair in various forms of organs and tissues damage [154].

The rats’ dental canals treated with DPSC-CM showed the formation of connective tissue, allowing for the detection of scattered blood vessels. Most of them were covered with blood cells, inflammatory cells, and collagen fibers. These data revealed that DPSC-CM were able to perform slight root restructuring of the dental canal. An immunopositively reaction against VEGF receptor 2 has been reported in newly formed tissues associated with the developmental stage of blood vessels [155]. Recently, a study demonstrated that association of DPSC-CM and mineral trioxide aggregate (MTA) revealed favorable effects on direct pulp capping in rats, greater than those of MTA when applied alone. Importantly, improvements were observed in the rate of dentin bridge formation, the morphological quality of these newly formed hard tissues, and primarily the control of inflammation in the pulp tissue [156].

13. Relationship between DPSC-CM and Exosomes

Primarily, the DPSC-CM comprises cytokines and a miniscule number of DPSC-secreted exosomes, which is easier to obtain in cytokines (Table 1). Hence, DPSC-CM is assumed to be nonimmunogenic, promoting their use in the same or different animal species. The action mechanism of the secreted factors mainly regulates the balance between these anti- and pro-inflammatory cytokines in a specific tissue (Table 2).

### Table 2. Therapeutic effects of DPSC-CM for various diseases.

| Type                  | Disease                                      | Animal Model                          | Administration Method | Mechanism                                                                 | Reference        |
|-----------------------|----------------------------------------------|---------------------------------------|-----------------------|---------------------------------------------------------------------------|------------------|
| Cerebrovascular disease | Forcal cerebral ischemia                      | Cerebral ischemia model (Sprague-Dawley rats) | Intranasal injection  | Induction of activated M2-type microglia                                 | Inoue T et al. [32] |
|                       | Aneurysmal subarachnoid hemorrhage            | Experimental aSAH model (Wistar rats)   | Intrathecal injection | Inhibitor for MMP-3 and 9 by TIMP-2                                       | Chen TF et al. [35] |
| Heart disease         | Myocardial infarction                         | Myocardial ischemia-reperfusion injury model (C57BL/6J mice) | Intravenous injection | Reduction of cardiomyocyte death and suppression of inflammatory responses | Yamaguchi S et al. [46] |
| Lung disease          | Acute lung injury                             | Bleomycin-induced acute lung injury model (C57BL/6J mice) | Intravenous injection | Induction of M2 macrophage differentiation                                | Wakayama H et al. [53] |
| Liver disease         | Liver fibrosis                                | Carbon tetrachloride (CCl4)-induced liver fibrosis model (C57BL/6J mice) | Intravenous injection | Induction of the MMP-13+ restorative hepatic macrophages                   | Hirata M et al. [61] |
|                       | Acute liver failure                           | D-galactosamine-induced acute liver failure model (Sprague-Dawley rats) | Intravenous injection | Induction of an anti-inflammatory M2 environment and activation of adult LPCs | Matsushita Y et al. [62] |
| Eye disease           | Retinitis pigmentosa                         | C57BL/6 J mice with RPGR knockout      | Subretinal injection  | Anti-apoptotic activity                                                    | Li XX et al. [74]  |
| Neurological disorder | Spinal cord injury                            | Contusion model of spinal cord injury (Sprague-Dawley rats) | Injection into the injury epicenter | Induction of an M2-dominant neurorepairing microenvironment by ED-Siglec-9 and MCP-1 | Asadi-Golshan R et al. [82], Matsubara K et al. [83] |
|                       | Facial nerve injury                           | Facial nerves transaction model (Sprague-Dawley rats) | Local implantation with an atelocollagen sponge | Induction of the polarization of M2 macrophages by MCP-1/Siglec-9 | Kano F et al. [84] |
|                       | Parkinson’s disease                           | Parkinson’s disease model (Lewis rats)  | Intravenous injection | Upregulation of tyrosine hydroxylase expression                            | Chen YR et al. [87] |
Table 2. Cont.

| Type                  | Disease                                      | Animal Model                                                                 | Administration Method | Mechanism                                                                 | Reference                      |
|-----------------------|----------------------------------------------|-------------------------------------------------------------------------------|-----------------------|----------------------------------------------------------------------------|---------------------------------|
| Alzheimer’s disease   | Aβ1-40 peptide-induced Alzheimer’s disease model (imprinting control region mice) | Intranasal injection                                                        | Activated M2-type microglia | Mita T et al. [92]                                                          |
| Amyotrophic lateral sclerosis | Transgenic mice (B6SJ-L-Tg (SOD1G93A1 Gur/J)) expressing the human superoxide dismutase 1 (mSOD1<sup>G93A</sup>) mutation | Intraperitoneal injection                                                   | Directly protection of motor neurons | Wang J et al. [94]                                                          |
| Multiple sclerosis    | Experimental autoimmune encephalomyelitis (EAE) model (C57BL/6j mice) | Intravenous injection                                                        | Induction of M2 macrophage polarization through ED-Siglec-9 by interacting with the sialic acid-bound CCR2 | Shimojima C et al. [96]          |
| Autoimmune disease    | Sjögren’s syndrome                           | Nonobese diabetic (NOD) mice                                                 | Intravenous injection   | Induction of Tregs through the TGF-β/Smad pathway                           | Matsumura-Kawashima M et al. [30] |
|                       |                                              | Mouse mechanical stress-induced osteoarthritis model (Institute of Cancer Research mice) | Local injection         | Stimulation of endogenous cells to proliferate and replace the lost tissue | Lo Monaco M et al. [115]         |
|                       |                                              | Zoledronate-induced MRONJ model (Wistar rats)                                | Local injection         | Induced epithelial tissue formation by increasing vascular endothelial cells | Ogasawara N et al. [121]         |
| Bone and Cartilage disease |                                                          |                                                                                |                        |                                                                           | Abe F et al. [129]               |
|                       | Osteoarthritis                               |                                                                                |                        |                                                                           | Kushino H et al. [130]           |
|                       | Medication-related osteonecrosis of the jaw (MRONJ) |                                                                                |                        |                                                                           |                                 |
|                       | Diabetes mellitus                            | Streptozotocin-induced diabetic mice (C57BL/6j mice)                         | Intravenous injection   | Protection and encouragement of the propagation for β-cells                | Izumoto-Akita T et al. [141]     |
|                       | Diabetic polyneuropathy                      | Streptozotocin-induced diabetic rats (Sprague-Dawley rats)                   | Local injection into the hindlimb skeletal muscles | Angiogenesis and improvement of blood flow, anti-inflammatory action, and neuroprotective action | Makino E et al. [147] Kanada S et al. [148] Hata M et al. [149] |
| Dental disease        | Dental trauma                                 | Orthotopic transplantation model (Wistar rats)                               | Local injection with a collagen | Immunopositivity reaction for VEGF receptor 2, and mainly controlling pulp tissue inflammation | de Cara S et al. [155] Sarra G et al. [156] |

Exosome refers to a specific class of lipid-membrane-bound extracellular vesicles having a diameter of 40–150 nm. Subsequently, exosomes may be internalized by other cells, mainly by phagocytosis and fusion with the cell membrane and receptor–ligand interaction, allowing them to release their contents into the cytoplasm [157]. The exosomes' regenerative potential might be modulated by various mechanisms, including the prior exposure of the originating cell population to external stimuli [158]. However, the primary functional molecules of exosomes remain unclear, and currently, there is no unified dosage, method of administration, or storage scheme for cell-free therapy; thus, further systematic and extensive research is required to resolve these problems.

14. Current Limitation and Perspective

Since the CM also contains several waste products produced by cell metabolism, there are limits to its therapeutic application [159]. Additionally, there is a difference in the effect of the obtained CM depending on the condition of the cell culture. To apply the CM to clinical practice, it is necessary to mass-produce it using an automatic culture device.

15. Conclusions

Figure 1 and Table 2 summarize the relevant reports. DPSC-CM may be more relevant for cell-free treatment of immune- and inflammation-related diseases. Nevertheless, studies evaluating the immunomodulatory and anti-inflammatory effects of DPSC-CM are still insufficient compared with BMSC-CM. Additional studies should focus on the full eluci-
validation of the critical role and the associated mechanisms of DPSC-CM immunomodulatory properties.

14. Current Limitation and Perspective

Since the CM also contains several waste products produced by cell metabolism, there are limits to its therapeutic application [159]. Additionally, there is a difference in the effect of the obtained CM depending on the condition of the cell culture. To apply the CM to clinical practice, it is necessary to mass-produce it using an automatic culture device.

15. Conclusions

Figure 1 and Table 2 summarize the relevant reports. DPSC-CM may be more relevant for cell-free treatment of immune- and inflammation-related diseases. Nevertheless, studies evaluating the immunomodulatory and anti-inflammatory effects of DPSC-CM are still insufficient compared with BMMSC-CM. Additional studies should focus on the full elucidation of the critical role and the associated mechanisms of DPSC-CM immunomodulatory properties.

Figure 1. Schematic representation of therapeutic potential summary of DPSC-CM.

Author Contributions: The data was collected by K.O., M.M.-K., T.K. and A.Y. The study was conducted by S.N. The manuscript was written by K.O. and M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported partly by Grants-in-Aid for Scientific Research (JP22K10221, JP20K18671 and JP20K23113) of the Ministry of Education, Culture, Sports, Science and Technology of Japan, including a research grant by SAITAS, Ikeda Scientific Co., ltd., and a research grant by The Uehara Memorial Foundation.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.
Abbreviations

DPSCs: dental pulp derived stem cells; MSCs: mesenchymal stem cells; DPSC-CM: secreted factors of dental pulp derived stem cells; STRO-1: stromal precursor antigen-1; VCAM-1: vascular cell adhesion molecule-1; SH2: Src homology 2; GD2: ganglioside 2; SSEA4: stage-specific embryonic antigen 4; BMMSCs: bone marrow derived mesenchymal stem cells; BMMSC-CM: secreted factors of bone marrow derived mesenchymal stem cell; IL: interleukin; TGF: transforming growth factor; HGF: hepatocyte growth factor; NCAM-1: neural cell adhesion molecule-1; ED-Siglec-9: ectodomain of sialic acid-binding Ig-like lectin-9; MMP: matrix metalloproteinase; NT-3: neurophin-3; BDNF: brain-derived neurotrophic factor; CNS: central nervous system; TIMP: tissue inhibitor of metalloproteinase; MI: myocardial infarction; I/R: ischemia-reperfusion; LPS: lipopolysaccharide; ARDS: acute respiratory distress syndrome; BLM: bleomycin; ALF: acute liver injury; ALF: acute liver failure; LPCs: liver stem/progenitor cells; LF: liver fibrosis; SCF: stem cell factors; IGFBP: insulin-like growth factor-binding protein; VEGF: vascular endothelial growth factor; EGVEGF: endocrine-gland-derived vascular endothelial growth factor; RP: retinitis pigmentosa; SCI: spinal cord injury; MCP-1: monocyte chemoattractant protein-1; FNI: facial nerve injury; PD: Parkinson’s disease; AD: Alzheimer’s disease; Aβ: amyloid; ALS: amyotrophic lateral sclerosis; MS: multiple sclerosis; EAE: experimental autoimmune encephalomyelitis; PBMCs: peripheral blood mononuclear cells; TRLS: toll-like receptors; NOD mice: non-obese diabetic mice; SS: Sjögren’s syndrome; SMGs: salivary glands; Treg: regulatory T cells; AC: articular cartilage; OA: osteoarthritis; MCA: matrix-induced autologous chondrocyte implantation; TMJ: temporomandibular joint; TMJOA: temporomandibular joint osseointegration; BP: bisphosphonate; DNP: diabetic polyneuropathy; STZ: streptozotocin; MTA: mineral trioxide aggregate.

References

1. Gronthos, S.; Mankani, M.; Brahim, J.; Robey, P.G.; Shi, S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc. Natl. Acad. Sci. USA 2000, 97, 13625–13630. [CrossRef] [PubMed]
2. Yamamura, T. Differentiation of pulp al cells and inductive influences of various matrices with reference to pulpal wound healing. J. Dent. Res. 1985, 64, 530–540. [CrossRef] [PubMed]
3. Mattei, V.; Martellucci, S.; Pulcini, F.; Santilli, F.; Sorice, M.; Delle Monache, S. Regenerative Potential of DPSCs and Revascularization: Direct, Paracrine or Autocrine Effect? Stem Cell Res. Rep. 2021, 17, 1635–1646. [CrossRef] [PubMed]
4. Gang, E.J.; Bosnakovski, D.; Figueiredo, C.A.; Visser, J.W.; Perlingeiro, R.C. SSEA-4 identifies mesenchymal stem cells from bone marrow. Blood 2007, 109, 1743–1751. [CrossRef] [PubMed]
5. Martinez, C.; Hofmann, T.; Marino, R.; Dominici, M.; Horwitz, E.M. Human bone marrow mesenchymal stromal cells express the neural ganglioside GD2: A novel surface marker for the identification of MSCs. Blood 2007, 109, 4245–4248. [CrossRef] [PubMed]
6. Bakopoulou, A.; Apatzidou, D.; Aggelidou, E.; Gousoupolou, E.; Leyhausen, G.; Volk, J.; Kritas, P.; Geurtsen, W. Isolation and prolonged expansion of oral mesenchymal stem cells under clinical-grade, GMP-compliant conditions differentially affects “stemness” properties. Stem Cell Res. Ther. 2017, 8, 247. [CrossRef] [PubMed]
7. Qiu, Z.; Lin, S.; Hu, X.; Zeng, J.; Xiao, T.; Ke, Z.; Lv, H. Involvement of miR-146a-5p/neurogenic locus notch homolog protein 1 in the proliferation and differentiation of STRO-1(+) human dental pulp stem cells. Eur. J. Oral. Sci. 2019, 127, 294–303. [CrossRef] [PubMed]
8. Petrenko, Y.; Vackova, I.; Kubinova, S. A Comparative Analysis of Multipotent Mesenchymal Stromal Cells derived from Different Sources, with a Focus on Neuroregenerative Potential. Sci. Rep. 2020, 10, 4290. [CrossRef] [PubMed]
9. Uchi, T.; Nakagawa, T. Mesenchymal stem cell-based tissue regenerative therapies for periodontitis. Regen. Ther. 2020, 14, 72–78. [CrossRef] [PubMed]
10. Jo, H.; Brito, S.; Kwak, B.M.; Park, S.; Lee, M.G.; Bin, B.H. Applications of Mesenchymal Stem Cells in Skin Regeneration and Rejuvenation. Int. J. Mol. Sci. 2021, 22, 2410. [CrossRef]
11. Ulpiano, C.; da Silva, C.L.; Monteiro, G.A. Mesenchymal Stromal Cells (MSCs): A Promising Tool for Cell-Based Angiogenic Therapy. Curr. Gene Therapy. 2021, 21, 382–405. [CrossRef] [PubMed]
12. Das, M.; Mayilsamy, K.; Mohapatra, S.S.; Mohapatra, S. Mesenchymal stem cell therapy for the treatment of traumatic brain injury: Progress and prospects. Rev. Neurosci. 2019, 30, 839–855. [CrossRef] [PubMed]
13. Cao, Y.; Ji, C.; Lu, L. Mesenchymal stem cell therapy for liver fibrosis/cirrhosis. Ann. Transl. Med. 2020, 8, 562. [CrossRef] [PubMed]
14. Sandona, M.; Di Pietro, L.; Esposito, F.; Ventura, A.; Silini, A.R.; Parolini, O.; Saccone, V. Mesenchymal Stromal Cells and Their Secretome: New Therapeutic Perspectives for Skeletal Muscle Regeneration. Front. Bioeng. Biotechnol. 2021, 9, 652970. [CrossRef] [PubMed]
15. Van Nguyen, T.T.; Vu, N.B.; Van Pham, P. Mesenchymal Stem Cell Transplantation for Ischemic Diseases: Mechanisms and Challenges. *Tissue Eng. Regen. Med.* 2021, 18, 587–611. [CrossRef]

16. Goetherstrom, C.; Walther-Jallow, L. Stem Cell Therapy as a Treatment for Osteogenesis Imperfecta. *Curr. Osteoporos. Rep.* 2020, 18, 337–343. [CrossRef]

17. Young, F.; Sloan, A.; Song, B. Dental pulp stem cells and their potential roles in central nervous system regeneration and repair. *J. Neurosci. Res.* 2013, 91, 1383–1393. [CrossRef]

18. Ahmed Nel, M.; Murakami, M.; Hirose, Y.; Nakashima, M. Therapeutic Potential of Dental Pulp Stem Cell Secretome for Alzheimer’s Disease Treatment: An In Vitro Study. *Stem Cells Int.* 2016, 2016, 8102478. [CrossRef]

19. Kim, H.J.; Cho, Y.A.; Lee, Y.M.; Lee, S.Y.; Bae, W.J.; Kim, E.C. PIN1 Suppresses the Hepatic Differentiation of Pulp Stem Cells via Wnt5a. *J. Dent. Res.* 2016, 95, 1415–1424. [CrossRef]

20. Mead, B.; Logan, A.; Berry, M.; Leadbeater, W.; Scheven, B.A. Concise Review: Dental Pulp Stem Cells: A Novel Cell Therapy for Retinal and Central Nervous System Repair. *Stem Cells* 2017, 35, 61–67. [CrossRef]

21. Nicola, F.D.C.; Marques, M.R.; Odorczyk, F.; Arcego, D.M.; Petenuzzo, L.; Aristimunha, D.; Vizuete, A.; Sanches, E.F.; Pereira, D.P.; Maurmann, N.; et al. Neuroprotector effect of stem cells from human exfoliated deciduous teeth transplanted after traumatic spinal cord injury involves inhibition of early neuronal apoptosis. *Brain Res.* 2017, 1663, 95–105. [CrossRef]

22. Ide, C.; Nakai, Y.; Nakano, N.; Geo, T.B.; Yamada, Y.; Endo, K.; Noda, T.; Saito, F.; Suzuki, Y.; Fukushima, M.; et al. Bone marrow stromal cell transplantation for treatment of sub-acute spinal cord injury in the rat. *Brain Res.* 2010, 1332, 32–47. [CrossRef]

23. Osugi, M.; Katagiri, W.; Yoshimi, R.; Inukai, T.; Hibi, H.; Ueda, M. Conditioned media from mesenchymal stem cells enhanced bone regeneration in rat calvarial bone defects. *Tissue Eng. Part A* 2012, 18, 1479–1489. [CrossRef]

24. Inukai, T.; Katagiri, W.; Yoshimi, R.; Osugi, M.; Kawai, T.; Hibi, H.; Ueda, M. Novel application of stem cell-derived factors for periodontal regeneration. *Biochem. Biophys. Res. Commun.* 2013, 430, 763–768. [CrossRef] [PubMed]

25. Kawai, T.; Katagiri, W.; Osugi, M.; Sugimura, Y.; Hibi, H.; Ueda, M. Secretomes from bone marrow-derived mesenchymal stem cells enhance periodontal tissue regeneration. *Cytotherapy* 2015, 17, 369–381. [CrossRef]

26. Ogata, K.; Katagiri, W.; Osugi, M.; Kawai, T.; Sugimura, Y.; Hibi, H.; Nakamura, S.; Ueda, M. Evaluation of the therapeutic effects of conditioned media from mesenchymal stem cells in a rat biphosphonate-related osteonecrosis of the jaw-like model. *Bone* 2015, 74, 95–105. [CrossRef] [PubMed]

27. Sugimura-Wakayama, Y.; Katagiri, W.; Osugi, M.; Kawai, T.; Ogata, K.; Sakaguchi, K.; Hibi, H. Peripheral Nerve Regeneration by Secretomes of Stem Cells from Human Exfoliated Deciduous Teeth. *Stem Cells Dev.* 2015. [CrossRef]

28. Yamada, Y.; Nakamura-Yamada, S.; Umemura-Kubota, E.; Baba, S. Diagnostic Cytokines and Comparative Analysis Secreted from Exfoliated Deciduous Teeth, Dental Pulp, and Bone Marrow Derived Mesenchymal Stem Cells for Functional Cell-Based Therapy. *Int. J. Mol. Sci.* 2019, 20, 5900. [CrossRef] [PubMed]

29. Bousnaki, M.; Bakoupolou, A.; Pich, A.; Papachristou, E.; Krits, A.; Koidis, P. Mapping the Secretome of Dental Pulp Stem Cells Under Variable Microenvironmental Conditions. *Stem Cell Rev. Rep.* 2021, 18, 1372–1407. [CrossRef] [PubMed]

30. Matsumura-Kawashima, M.; Ogata, K.; Moriyama, M.; Murakami, Y.; Kawado, T.; Nakamura, S. Secreted factors from dental pulp stem cells improve Sjögren’s syndrome via regulatory T cell-mediated immunosuppression. *Stem Cell Res. Ther.* 2021, 12, 182. [CrossRef]

31. Ogata, K.; Matsumura-Kawashima, M.; Moriyama, M.; Kawado, T.; Nakamura, S. Dental pulp-derived stem cell-conditioned media attenuates secondary Sjögren’s syndrome via suppression of inflammatory cytokines in the submandibular glands. *Regen. Ther.* 2021, 16, 73–80. [CrossRef] [PubMed]

32. Inoue, T.; Sugiyama, M.; Hattori, H.; Wakita, H.; Wakabayashi, T.; Ueda, M. Stem cells from human exfoliated deciduous tooth-derived conditioned medium enhance recovery of focal cerebral ischemia in rats. *Tissue Eng. Part A* 2013, 19, 24–29. [CrossRef]

33. Yamagata, M.; Yamamoto, A.; Kako, E.; Kaneko, N.; Matsubara, K.; Sakai, K.; Sawamoto, K.; Ueda, M. Human dental pulp-derived stem cells protect against hypoxic-ischemic brain injury in neonatal mice. *Stroke* 2013, 44, 551–554. [CrossRef]

34. Yamamoto, A.; Sakai, K.; Matsubara, K.; Kano, F.; Ueda, M. Multifaceted neuro-regenerative activities of human dental pulp stem cells for functional recovery after spinal cord injury. *Neurosci. Res.* 2014, 78, 16–20. [CrossRef] [PubMed]

35. Chen, T.F.; Chen, K.W.; Chien, Y.; Lai, Y.H.; Hsieh, S.T.; Ma, H.Y.; Wang, K.C.; Shiau, C.Y. Dental Pulp Stem Cells Alleviate Subarachnoid Hemorrhage-Induced Neuroinflammation and Ischemic Neurological Deficits. *Int. J. Mol. Sci.* 2019, 20, 3747. [CrossRef] [PubMed]

36. Sakai, K.; Yamamoto, A.; Matsubara, K.; Nakamura, S.; Naruse, M.; Yamagata, M.; Sawamoto, K.; Tauchi, R.; Wako, N.; Imagama, S.; et al. Human dental pulp stem cells promote locomotor recovery after complete transection of the rat spinal cord by multiple neuro-regenerative mechanisms. *J. Clin. Investig.* 2012, 122, 80–90. [CrossRef] [PubMed]

37. Aliaghaei, A.; Boroujeni, M.E.; Ahmadi, H.; Bayat, A.H.; Tavirani, M.R.; Abdollahifar, M.A.; Poyyafar, M.H.; Mansouri, V. Dental pulp stem cell transplantation ameliorates motor function and prevents cerebellar atrophy in rat model of cerebellar ataxia. *Cell Tissue Res.* 2019, 376, 179–187. [CrossRef] [PubMed]

38. Willis, C.M.; Nicaise, A.M.; Peruzzotti-Jametti, L.; Pluchino, S. The neural stem cell secretome and its role in brain repair. *Brain Res.* 2020, 1729, 146615. [CrossRef]
39. Luzuriaga, J.; Polo, Y.; Pastor-Alonso, O.; Pardo-Rodriguez, B.; Larranaga, A.; Unda, F.; Sarasua, J.R.; Pineda, J.R.; Ibarretxe, G. Advances and Perspectives in Dental Pulp Stem Cell Based Neuroregeneration Therapies. *Int. J. Mol. Sci.* 2021, 22, 3546. [CrossRef]

40. Iademola, C.; Buckwalter, M.S.; Anrather, J. Immune responses to stroke: Mechanisms, modulation, and therapeutic potential. *J. Clin. Invest.* 2020, 130, 2777–2788. [CrossRef]

41. Kawabori, M.; Shichinohe, H.; Kuroda, S.; Houkin, K. Clinical Trials of Stem Cell Therapy for Cerebral Ischemic Stroke. *Int. J. Mol. Sci.* 2020, 21, 7380. [CrossRef]

42. Nie, G.; Wen, X.; Liang, X.; Zhao, H.; Li, Y.; Lu, J. Additional evidence supports association of common genetic variants in MMP3 and TIMP2 with increased risk of chronic Achilles tendinopathy susceptibility. *J. Sci. Med. Sport* 2019, 22, 1074–1078. [CrossRef] [PubMed]

43. Hu, B.H.; Cai, Q.; Hu, Z.; Patel, M.; Bard, J.; Jamison, J.; Coling, D. Metalloproteinases and their associated genes contribute to the functional integrity and noise-induced damage in the cochlear sensory epithelium. *J. Neurosci. Off. J. Soc. Neurosci.* 2012, 32, 14927–14941. [CrossRef] [PubMed]

44. Markwerth, P.; Bajanoowski, T.; Tzimas, I.; Dettmeyer, R. Sudden cardiac death-update. *Int. J. Leg. Med.* 2021, 135, 483–495. [CrossRef] [PubMed]

45. Heusch, G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat. Rev. Cardiol.* 2020, 17, 773–789. [CrossRef] [PubMed]

46. Yamaguchi, S.; Shibata, R.; Yamamoto, N.; Nishikawa, M.; Hibi, H.; Tanigawa, T.; Ueda, M.; Murohara, T.; Yamamoto, A. Dental pulp-derived stem cell conditioned medium reduces cardiac injury following ischaemia-reperfusion. *Sci. Rep.* 2015, 5, 16295. [CrossRef] [PubMed]

47. Sowa, K.; Nito, C.; Nakajima, M.; Suda, S.; Nishiyama, Y.; Sakamoto, Y.; Nitahara-Kasahara, Y.; Nakamura-Takahashi, A.; Ueda, M.; Kimura, K.; et al. Impact of Dental Pulp Stem Cells Overexpressing Hepatocyte Growth Factor after Cerebral Ischemia/Reperfusion in Rats. *Mol. Methods Clin. Dev.* 2018, 10, 281–290. [CrossRef]

48. Cheng, P.; Li, S.; Chen, H. Macrophages in Lung Injury, Repair, and Fibrosis. *Cells* 2021, 10, 436. [CrossRef]

49. He, Y.Q.; Zhou, C.C.; Yu, L.Y.; Wang, L.; Deng, J.L.; Tao, Y.L.; Zhang, F.; Chen, W.S. Natural product derived phytochemicals in managing acute lung injury by multiple mechanisms. *Pharm. Res.* 2021, 163, 105224. [CrossRef]

50. Murray, P.J.; Wynn, T.A. Protective and pathogenic functions of macrophage subsets. *Nat. Rev. Immunol.* 2011, 11, 723–737. [CrossRef]

51. Feng, Y.; Xu, Q.; Yang, Y.; Shi, W.; Meng, W.; Zhang, H.; He, X.; Sun, M.; Chen, Y.; Zhao, J.; et al. The therapeutic effects of bone marrow-derived mesenchymal stromal cells in the acute lung injury induced by sulfur mustard. *Stem Cell Res. Ther.* 2019, 10, 90. [CrossRef] [PubMed]

52. Ross, E.A.; Devitt, A.; Johnson, J.R. Macrophages: The Good, the Bad, and the Gluttony. *Front. Immunol.* 2021, 12, 708186. [CrossRef]

53. Wakayama, H.; Hashimoto, N.; Matsushita, Y.; Matsubara, K.; Yamamoto, N.; Hasegawa, Y.; Ueda, M.; Yamamoto, A. Factors secreted from dental pulp stem cells show multifaceted benefits for treating acute lung injury in mice. *Cytotherapy* 2015, 17, 1119–1129. [CrossRef] [PubMed]

54. Ionescu, L.; Byrne, R.N.; van Haften, T.; Vadelv, A.; Alphonse, R.S.; Rey-Parra, G.J.; Weissmann, G.; Hall, A.; Eaton, F.; Thebaud, B. Stem cell conditioned medium improves acute lung injury in mice: In vivo evidence for stem cell paracrine action. *Am. J. Physiol. Lung. Cell Mol. Physiol.* 2012, 303, L967–L977. [CrossRef] [PubMed]

55. Stravitz, R.T.; Lee, W.M. Acute liver failure. *Lancet* 2019, 394, 869–881. [CrossRef]

56. Miyajima, A.; Tanaka, M.; Itoh, T. Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming. *Cell Stem Cell* 2014, 14, 561–574. [CrossRef]

57. Michalopoulos, G.K.; Bhushan, B. Liver regeneration: Biological and pathological mechanisms and implications. *Nat. Rev. Gastroenterol. Hepatol.* 2021, 18, 40–55. [CrossRef]

58. Kisseleva, T.; Brenner, D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat. Rev. Gastroenterol. Hepatol.* 2021, 18, 151–166. [CrossRef]

59. Hu, C.; Zhao, L.; Zhang, L.; Bao, Q.; Li, L. Mesenchymal stem cell-based cell-free strategies: Safe and effective treatments for liver injury. *Stem Cell Res. Ther.* 2020, 11, 377. [CrossRef]

60. Chinnici, C.M.; Russelli, G.; Bulati, M.; Miceli, V.; Gallo, A.; Busa, R.; Tinnirello, R.; Conalda, P.G.; Iannolo, G. Mesenchymal stromal cell secretome in liver failure: Perspectives on COVID-19 infection treatment. *World J. Gastroenterol.* 2020, 26, 17, 1905–1919. [CrossRef] [PubMed]

61. Hirata, M.; Ishigami, M.; Matsushita, Y.; Ito, T.; Hattori, H.; Hibi, H.; Goto, H.; Ueda, M.; Yamamoto, A. Multifaceted Therapeutic Benefits of Factors Derived from Dental Pulp Stem Cells for Mouse Liver Fibrosis. *Stem Cells Transl. Med.* 2016, 5, 1416–1424. [CrossRef] [PubMed]

62. Matsushita, Y.; Ishigami, M.; Matsubara, K.; Kondo, M.; Wakayama, H.; Goto, H.; Ueda, M.; Yamamoto, A. Multifaceted therapeutic benefits of factors derived from human exfoliated deciduous teeth for acute liver failure in rats. *J. Tissue Eng. Regen. Med.* 2017, 11, 1888–1896. [CrossRef] [PubMed]
63. Okano, J.; Shiota, G.; Matsumoto, K.; Yasui, S.; Kurimasa, A.; Hisatome, I.; Steinberg, P.; Murawaki, Y. Hepatocyte growth factor exerts a proliferative effect on oval cells through the PI3K/AKT signaling pathway. Biochem. Biophys. Res. Commun. 2003, 309, 298–304. [CrossRef] [PubMed]

64. Moumen, A.; Ieraci, A.; Patane, S.; Sole, C.; Comella, J.X.; Dono, R.; Maina, F. Met signals hepatocyte survival by preventing Fas-triggered FLIP degradation in a PI3K-Akt-dependent manner. Hepatology 2007, 45, 1210–1217. [CrossRef]

65. Hu, B.; Colletti, L.M. Stem cell factor and e-kit are involved in hepatic recovery after acetaminophen-induced liver injury in mice. Am. J. Physiol. Gastrointest. Liver Physiol. 2008, 295, G45–G53. [CrossRef]

66. Leu, J.I.; Crissey, M.A.; Taub, R. Massive hepatic apoptosis associated with TGF-beta1 activation after Fas ligand treatment of IGF binding protein-1-deficient mice. J. Clin. Investig. 2003, 111, 129–139. [CrossRef]

67. Duarte, S.; Hamada, T.; Kuriyama, N.; Busuttil, R.W.; Coito, A.J. TIMP-1 deficiency leads to lethal partial hepatic ischemia and reperfusion injury. Hepatology 2012, 56, 1074–1085. [CrossRef]

68. Gao, X.; Xu, Z. Mechanisms of action of angiojenin. Acta Biochim. Biophys. Sin. 2008, 40, 619–624. [CrossRef]

69. Chen, H.; Tang, S.; Liao, J.; Liu, M.; Lin, Y. VEGF165 gene-modified human umbilical cord blood mesenchymal stem cells protect against acute liver failure in rats. J. Gene Med. 2021, 23, e3369. [CrossRef]

70. Lin, Y.; Dong, M.Q.; Liu, Z.M.; Xu, M.; Huang, Z.H.; Liu, H.J.; Gao, Y.; Zhou, W.J. A strategy of vascular-targeted therapy for liver fibrosis. Hepatology 2021. [CrossRef]

71. Roca, H.; Varsos, Z.S.; Sud, S.; Craig, M.J.; Ying, C.; Pienta, K.J. CCL2 and interleukin-6 promote survival of human CD11b+ peripheral blood mononuclear cells and induce M2-type macrophage polarization. J. Biol. Chem. 2009, 284, 34342–34354. [CrossRef] [PubMed]

72. Newton, F.; Megaw, R. Mechanisms of Photoreceptor Death in Retinitis Pigmentosa. Genes 2020, 11, 1120. [CrossRef] [PubMed]

73. Sahel, J.A.; Boulanger-Seemana, E.; Pagot, C.; Arleo, A.; Galluppi, F.; Martel, J.N.; Esposti, S.D.; Delaux, A.; de Saint Aubert, J.B.; de Montleau, C.; et al. Partial recovery of visual function in a blind patient after optogenetic therapy. Nat. Med. 2021, 27, 1223–1229. [CrossRef] [PubMed]

74. Li, X.X.; Yuan, X.J.; Zhai, Y.; Yu, S.; Jia, R.X.; Yang, L.P.; Ma, Z.Z.; Zhao, Y.M.; Wang, Y.X.; Ge, L.H. Treatment with Stem Cells from Human Exfoliated Deciduous Teeth Induces the Integration of Dental Pulp Stem Cells and Their Derived Conditioned Medium Improves Retinal Visual Function and Delays the Degeneration of Photoreceptors. Stem Cells Dev. 2019, 28, 1514–1526. [CrossRef]

75. Bray, A.F.; Cevallos, R.R.; Gazarian, K.; Lamas, M. Human dental pulp stem cells respond to cues from the rat retina and differentiate to express the retinal neuronal marker rhodopsin. Neuroscience 2014, 280, 142–155. [CrossRef] [PubMed]

76. Zrzavy, T.; Schwaiger, C.; Wimmer, I.; Berger, T.; Bauer, J.; Butovsky, O.; Schwab, J.M.; Lassmann, H.; Hoftberger, R. Acute and non-resolving inflammation associate with oxidative injury after human spinal cord injury. Brain 2021, 144, 144–161. [CrossRef]

77. Devanney, N.A.; Stewart, A.N.; Genzel, J.C. Microglia and macrophage metabolism in CNS injury and disease: The role of immunometabolism in neurodegeneration and neurotrauma. Exp. Neurol. 2020, 329, 113310. [CrossRef]

78. Tan, G.; Qian, D.; Wang, X.; Zhou, Z.; Liu, W.; Zhu, T.; Ning, B.; Qian, Y.; Zhou, W.; et al. Parthenolide promotes the repair of spinal cord injury by modulating M1/M2 polarization via the NF-kappaB and STAT 1/3 signaling pathway. Cell Death Discov. 2020, 6, 97. [CrossRef]

79. Kobashi, S.; Terashima, T.; Katagi, M.; Nakae, Y.; Okano, J.; Suzuki, Y.; Urushitani, M.; Kojima, H. Transplantation of M2-Deviated Microglia Promotes Recovery of Motor Function after Spinal Cord Injury in Mice. Mol. Ther. 2020, 28, 254–265. [CrossRef]

80. Zheng, Q.; Zhang, J.; Zuo, X.; Sun, J.; Liang, Z.; Hu, X.; Wang, Z.; Li, K.; Song, J.; Ding, T.; et al. Photobiomodulation Promotes Neuronal Axon Regeneration After Oxidative Stress and Induces a Change in Polarization from M1 to M2 in Macrophages via Stimulation of CCL2 in Neurons: Relevance to Spinal Cord Injury. J. Mol. Neurosci. 2021, 71, 1290–1300. [CrossRef]

81. Zhang, J.; Lu, X.; Feng, G.; Gu, Z.; Sun, Y.; Bao, G.; Xu, G.; Ly, U.; Chen, J.; Xu, L.; et al. Chitosan scaffolds induce human dental pulp stem cells to neural differentiation: Potential roles for spinal cord injury repair. Cell Res. 2016, 36, 129–142. [CrossRef] [PubMed]

82. Asadi-Golshan, R.; Razban, V.; Mirzaei, E.; Rahmanian, A.; Khajeh, S.; Mostafavi-Pour, Z.; Dehghani, F. Sensory and Motor Behavior Evidences Supporting the Usefulness of Conditioned Medium from Dental Pulp-Derived Stem Cells in Spinal Cord Injury in Rats. Asian Spine J. 2018, 12, 785–793. [CrossRef] [PubMed]

83. Matsubara, K.; Matsushita, Y.; Sakai, K.; Kano, F.; Kondo, M.; Noda, M.; Hashimoto, N.; Imagama, S.; Ishiguro, N.; Suzumura, A.; et al. Secreted ectodomain of sialic acid-binding Ig-like lectin-9 and monocyte chemotactic protein-1 promote recovery after spinal cord injury by altering macrophage polarity. J. Neurosci. Off. J. Soc. Neurosci. 2015, 35, 2452–2464. [CrossRef]

84. Kano, F.; Matsubara, K.; Ueda, M.; Hibi, H.; Yamamoto, A. Secreted Ectodomain of Sialic Acid-Binding Ig-Like Lectin-9 and Monocyte Chemotactic Protein-1 Synergistically Regenerate Transected Rat Peripheral Nerves by Altering Macrophage Polarity. Stem Cells 2017, 35, 641–653. [CrossRef] [PubMed]

85. Pajares, M.; Rojo, A.I.; Manda, G.; Bosca, L.; Cuadrado, A. Inflammation in Parkinson’s Disease: Mechanisms and Therapeutic Implications. Cells 2020, 9, 1687. [CrossRef]

86. Bloem, B.R.; Okun, M.S.; Klein, C. Parkinson’s disease. Lancet 2021, 397, 2284–2303. [CrossRef]

87. Chen, Y.R.; Lai, P.L.; Chien, Y.; Lee, P.H.; Lai, Y.H.; Ma, H.L.; Shiau, C.Y.; Wang, K.C. Improvement of Impaired Motor Functions by Human Dental Exfoliated Deciduous Teeth Stem Cell-Derived Factors in a Rat Model of Parkinson’s Disease. Int. J. Mol. Sci. 2020, 21, 3807. [CrossRef]
88. Abeyesinghe, A.; Deshapriya, R.; Udawatte, C. Alzheimer’s disease: A review of the pathophysiological basis and therapeutic interventions. *Lif Sci.* 2020, 256, 117996. [CrossRef]
89. Sengoku, R. Aging and Alzheimer’s disease pathology. *Neuropathology* 2020, 40, 22–29. [CrossRef]
90. Lei, P.; Aytan, S.; Bush, A.I. The essential elements of Alzheimer’s disease. *J. Biol. Chem.* 2021, 296, 100105. [CrossRef]
91. Scheltens, P.; De Strooper, B.; Kivipelto, M.; Holstege, H.; Chetelat, G.; Teunissen, C.E.; Cummings, J.; van der Flier, W.M. Alzheimer’s disease. *Lancet* 2021, 397, 1577–1590. [CrossRef]
92. Mita, T.; Furukawa-Hibi, Y.; Takeuchi, H.; Hattori, H.; Yamada, K.; Hibi, H.; Ueda, M.; Yamamoto, A. Conditioned medium from the stem cells of human dental pulp improves cognitive function in a mouse model of Alzheimer’s disease. *Behav. Brain Res.* 2015, 293, 189–197. [CrossRef]
93. Norris, S.P.; Likanje, M.N.; Andrews, J.A. Amyotrophic lateral sclerosis: Update on clinical management. *Curr. Opin. Neurol.* 2020, 33, 641–648. [CrossRef][PubMed]
94. Wang, J.; Zuzzio, K.; Walker, C.L. Systemic Dental Pulp Stem Cell Secretome Therapy in a Mouse Model of Amyotrophic Lateral Sclerosis. *Brain Sci.* 2019, 9, 165. [CrossRef]
95. Asadi-Golshan, R.; Razban, V.; Mirzaei, E.; Rahmanian, A.; Khajeh, S.; Mostafavi-Pour, Z.; Dehghani, F. Efficacy of dental pulp-derived stem cells conditioned medium loaded in collagen hydrogel in spinal cord injury in rats: Stereological evidence. *J. Chem. Neuroanat.* 2021, 116, 101978. [CrossRef][PubMed]
96. Shimojima, C.; Takeuchi, H.; Jin, S.; Parajuli, B.; Hattori, H.; Suzumura, A.; Hibi, H.; Ueda, M.; Yamamoto, A. Conditioned Medium from the Stem Cells of Human Exfoliated Deciduous Teeth Ameliorates Experimental Autoimmune Encephalomyelitis. *J. Immunol.* 2016, 196, 4164–4171. [CrossRef][PubMed]
97. Liu, S.; Liu, F.; Zhou, Y.; Jin, B.; Sun, Q.; Guo, S. Immunosuppressive Property of MSCs Mediated by Cell Surface Receptors. *Front. Immunol.* 2020, 11, 1076. [CrossRef]
98. Kiselevskii, M.V.; Vlasenko, R.Y.; Stepanyan, N.G.; Shubina, I.Z.; Srdtikova, S.M.; Kirgizov, K.I.; Varfolomeeva, S.R. Secretome of Mesenchymal Bone Marrow Stem Cells: Is It Immunosuppressive or Proinflammatory? *Bull. Exp. Biol. Med.* 2021, 172, 250–253. [CrossRef][PubMed]
99. Krampera, M.; Glennie, S.; Dyson, J.; Scott, D.; Laylor, R.; Simpson, E.; Dazzi, F. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. *Blood* 2003, 101, 3722–3729. [CrossRef]
100. Sonoyama, W.; Liu, Y.; Yamaza, T.; Tuan, R.S.; Wang, S.; Shi, S.; Huang, G.T. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: A pilot study. *J. Endod.* 2008, 34, 166–171. [CrossRef]
101. Wada, N.; Menicanin, D.; Shi, S.; Bartold, P.M.; Gronthos, S. Immunomodulatory properties of human periodontal ligament stem cells. *J. Cell. Physiol.* 2009, 219, 667–676. [CrossRef][PubMed]
102. Iwasaki, A.; Medzhitov, R. Toll-like receptor control of the adaptive immune responses. *Nat. Immunol.* 2004, 5, 987–995. [CrossRef][PubMed]
103. Ji, L.; Bao, L.; Gu, Z.; Zhou, Q.; Liang, Y.; Zheng, Y.; Xu, Y.; Zhang, X.; Feng, X. Comparison of immunomodulatory properties of exosomes derived from bone marrow mesenchymal stem cells and dental pulp stem cells. *Immunol. Res.* 2019, 67, 432–442. [CrossRef][PubMed]
104. Lo Monaco, M.; Merckx, G.; Ratajczak, J.; Gervois, P.; Hilkens, P.; Clegg, P.; Bronckaers, A.; Vandeweerd, J.M.; Lambrits, I. Stem Cells for Cartilage Repair: Preclinical Studies and Insights in Translational Animal Models and Outcome Measures. *Stem Cells Int.* 2015, 2018, 907938. [CrossRef][PubMed]
105. Xu, L.; Li, Y. A Molecular Cascade Underlying Articular Cartilage Degeneration. *Curr. Drug Targets* 2020, 21, 838–848. [CrossRef]
106. Krych, A.J.; Saris, D.B.F.; Stuart, M.J.; Hacken, B. Cartilage Injury in the Knee: Assessment and Treatment Options. *J. Am. Acad. Orthop. Surg.* 2020, 28, 914–922. [CrossRef]
107. Andersson, J.K.; Hagert, E.; Britthberg, M. Cartilage Injuries and Posttraumatic Osteoarthritis in the Wrist: A Review. *Cartilage* 2021, 13, 156S–168S. [CrossRef]
108. Cole, B.J.; Redondo, M.L.; Cotter, E.J. Articular Cartilage Injuries of the Knee: Patient Health Literacy, Expectations for Management, and Clinical Outcomes. *Cartilage* 2021, 12, 139–145. [CrossRef]
109. Hu, Y.; Chen, X.; Wang, S.; Jing, Y.; Su, J. Subchondral bone microenvironment in osteoarthritis and pain. *Bone Res.* 2021, 9, 20. [CrossRef]
110. van den Bosch, M.H.J. Osteoarthritis and cartilage degeneration in review 2020: Biology. *Osteoarthr. Cartil.* 2021, 29, 143–150. [CrossRef]
111. Aydin, M.; Yorubulut, M.; Basarir, K.; Arikan, M.; Binnet, M.S. Matrix induced autologous chondrocyte implantation in the knee: Comparison between osteochondritis dissecans and osteonecrosis and effect of chondrocyte thickness on prognosis. *Acta Orthop. Traumatol. Turc.* 2020, 54, 66–73. [CrossRef]
112. Niemeyer, P.; Albrecht, D.; Anderley, S.; Angele, P.; Ateschrrang, A.; Aurich, M.; Baumann, M.; Bosch, U.; Erggelet, C.; Fickert, S.; et al. Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group “Clinical Tissue Regeneration” of the German Society of Orthopaedics and Trauma (DGOU). *Knee* 2016, 23, 426–435. [CrossRef]
113. Pareek, A.; Carey, J.L.; Reardon, P.J.; Peterson, L.; Stuart, M.J.; Krych, A.J. Long-Term Outcomes after Autologous Chondrocyte Implantation: A Systematic Review at Mean Follow-Up of 11.4 Years. *Cartilage* 2016, 7, 298–308. [CrossRef][PubMed]
114. Aae, T.F.; Randsborg, P.H.; Luras, H.; Aroen, A.; Lian, O.B. Microfracture is more cost-effective than autologous chondrocyte implantation: A review of level 1 and level 2 studies with 5 year follow-up. *Knee Surg. Sports Traumatol. Arthrosc.* 2018, 26, 1044–1052. [CrossRef]
142. Brissova, M.; Aamodt, K.; Brahmachary, P.; Prasad, N.; Hong, J.Y.; Dai, C.; Mellati, M.; Shostak, A.; Poffenberger, G.; Aramanda, R.; et al. Islet microenvironment, modulated by vascular endothelial growth factor-A signaling, promotes beta cell regeneration. *Cell Metab.* 2014, 19, 498–511. [CrossRef] [PubMed]

143. Elghazi, L.; Rachdi, L.; Weiss, A.J.; Cras-Meneur, C.; Bernal-Mizrachi, E. Regulation of beta-cell mass and function by the Akt/protein kinase B signalling pathway. *Diabetes Obes. Metab.* 2007, 9, 147–157. [CrossRef] [PubMed]

144. Matei, I.V.; Li, H.; Yaegaki, K. Hydrogen sulfide enhances pancreatic beta-cell differentiation from human tooth under normal and glucotoxic conditions. *Regen. Med.* 2017, 12, 125–141. [CrossRef]

145. Makinen, K.; Manninen, H.; Hedman, M.; Matsu, P.; Mussalo, H.; Alhava, E.; Yla-Herttuala, S. Increased vascularity detected by digital subtraction angiography after VEGF gene transfer to human lower limb artery: A randomized, placebo-controlled, double-blinded phase II study. *Mol. Ther.* 2002, 6, 127–133. [CrossRef]

146. Ropper, A.H.; Gorson, K.C.; Gooch, C.L.; Weinberg, D.H.; Pieczek, A.; Ware, J.H.; Kershen, J.; Rogers, A.; Simovic, D.; Schratzberger, P.; et al. Vascular endothelial growth factor gene transfer for diabetic polyneuropathy: A randomized, double-blinded trial. *Ann. Neurol.* 2009, 65, 386–393. [CrossRef] [PubMed]

147. Makino, E.; Nakamura, N.; Miyabe, M.; Ito, M.; Kanada, S.; Hata, M.; Saiki, T.; Kamiya, H.; Nakamura, J.; et al. Conditioned media from dental pulp stem cells improved diabetic polyneuropathy through anti-inflammatory, neuroprotective and angiogenic actions: Cell-free regenerative medicine for diabetic polyneuropathy. *J. Diabetes Investig.* 2019, 10, 1199–1208. [CrossRef]

148. Kanada, S.; Makino, E.; Nakamura, N.; Miyabe, M.; Ito, M.; Hata, M.; Yamauchi, T.; Sawada, N.; Kondo, S.; Saiki, T.; et al. Direct Comparison of Therapeutic Effects on Diabetic Polyneuropathy between Transplantation of Dental Pulp Stem Cells and Administration of Dental Pulp Stem Cell-Secreted Factors. *Int. J. Mol. Sci.* 2020, 21, 64. [CrossRef] [PubMed]

149. Hata, M.; Omi, M.; Kobayashi, Y.; Nakamura, N.; Miyabe, M.; Ito, M.; Ohno, T.; Imanishi, Y.; Himeno, T.; Kamiya, H.; et al. Sustainable Effects of Human Dental Pulp Stem Cell Transplantation on Diabetic Polyneuropathy in Streptozotocine-Induced Type 1 Diabetes Model Mice. *Cells* 2021, 10, 2473. [CrossRef]

150. Olsburgh, S.; Jacoby, T.; Krejci, I. Crown fractures in the permanent dentition: Pulpal and restorative considerations. *Dent. Traumatol.* 2002, 18, 103–115. [CrossRef] [PubMed]

151. Jones, L.C. Dental Trauma. *Oral Maxillofac. Surg. Clin. N. Am.* 2020, 32, 631–638. [CrossRef] [PubMed]

152. Laschke, M.W.; Harder, Y.; Amon, M.; Martin, I.; Farhadi, J.; Ring, A.; Torio-Padron, N.; Schramm, R.; Rucker, M.; Junker, D.; et al. Angiogenesis in tissue engineering: Breathing life into constructed tissue substitutes. *Tissue Eng.* 2006, 12, 2093–2104. [CrossRef] [PubMed]

153. Gunawardena, T.N.A.; Rahman, M.T.; Abdullah, B.J.J.; Abu Kasim, N.H. Conditioned media derived from mesenchymal stem cell cultures: The next generation for regenerative medicine. *J. Tissue Eng. Regen. Med.* 2019, 13, 569–586. [CrossRef] [PubMed]

154. Pawitan, J.A. Prospect of stem cell conditioned medium in regenerative medicine. *Biomed. Res. Int.* 2014, 2014, 965849. [CrossRef]

155. de Cara, S.; Origassa, C.S.T.; de Sa Silva, F.; Moreira, M.; de Almeida, D.C.; Pedroni, A.C.F.; Carvalho, G.L.; Cury, D.P.; Camara, N.O.S.; Marques, M.M. Angiogenic properties of dental pulp stem cells conditioned medium on endothelial cells in vitro and in rodent orthotopic dental pulp regeneration. *Heliyon* 2019, 5, e01560. [CrossRef]

156. Sarra, G.; Machado, M.E.L.; Caballero-Flores, H.V.; Moreira, M.S.; Pedroni, A.C.F.; Marques, M.M. Effect of human dental pulp stem cell conditioned medium in the dentin-pulp complex regeneration: A pilot in vivo study. *Tissue Cell* 2021, 72, 101536. [CrossRef]

157. Kalluri, R.; LeBleu, V.S. The biology, function, and biomedical applications of exosomes. *Science* 2020, 367. [CrossRef]

158. Cai, Y.; Li, J.; Jia, C.; He, Y.; Deng, C. Therapeutic applications of adipose cell-free derivatives: A review. *Stem Cell Res. Ther.* 2020, 11, 312. [CrossRef]

159. Chen, X.; Chen, A.; Woo, T.L.; Choo, A.B.; Reuveny, S.; Oh, S.K. Investigations into the metabolism of two-dimensional colony and suspended microcarrier cultures of human embryonic stem cells in serum-free media. *Stem Cells Dev.* 2010, 19, 1781–1792. [CrossRef]