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REVIEW ARTICLE

Mesenchymal Stem Cells of Dental Origin-Their Potential for Anti-inflammatory and Regenerative Actions in Brain and Gut Damage

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Abstract: Alzheimer's disease, Parkinson's disease, traumatic brain and spinal cord injury and neuroinflammatory multiple sclerosis are diverse disorders of the central nervous system. However, they are all characterized by various levels of inappropriate inflammatory/immune response along with tissue destruction. In the gastrointestinal system, inflammatory bowel disease (IBD) is also a consequence of tissue destruction resulting from an uncontrolled inflammation. Interestingly, there are many similarities in the immunopathomechanisms of these CNS disorders and the various forms of IBD. Since it is very hard or impossible to cure them by conventional manner, novel therapeutic approaches such as the use of mesenchymal stem cells, are needed. Mesenchymal stem cells have already been isolated from various tissues including the dental pulp and periodontal ligament. Such cells possess transdifferentiating capabilities for different tissue specific cells to serve as new building blocks for regeneration. But more importantly, they are also potent immunomodulators inhibiting proinflammatory processes and stimulating anti-inflammatory mechanisms.

The present review was prepared to compare the immunopathomechanisms of the above mentioned neurodegenerative, neurotraumatic and neuroinflammatory diseases with IBD. Additionally, we considered the potential use of mesenchymal stem cells, especially those from dental origin to treat such disorders. We conceive that such efforts will yield considerable advance in treatment options for central and peripheral disorders related to inflammatory degeneration.

Keywords: Alzheimer's disease, CNS damage, Crohn's disease, dental, immunomodulation, inflammation, inflammatory bowel disease, mesenchymal stem cells, multiple sclerosis, parkinson's disease, regeneration, spinal cord injury, traumatic brain injury, ulcerative colitis.

INTRODUCTION

Neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), traumatic disorders such as traumatic brain injury (TBI) and spinal cord injury (SCI) and neuroinflammatory diseases such as multiple sclerosis (MS) are very diverse illnesses of the central nervous system (CNS). The common features of these deteriorating disorders are the massive tissue destruction and various level of inflammation. It is very hard or impossible to treat them by conventional medical therapies since the nervous system has only a very limited ability to newly generate neurons and glial cells due to the limited number of necessary precursor cells, especially during inflammation when regenerative regulatory mechanisms are suppressed. Therefore, novel technologies such as application of stem cells hold a great promise for their cure in the nearby future. Present knowledge suggests that there are many similarities between CNS disorders and the various forms of inflammatory bowel disease (IBD). In fact, IBD is characterized by uncontrolled inflammation and damage to host tissues and its therapy constitutes a significant challenge for the physicians. Furthermore, both CNS disorders and IBD are becoming potential targets for stem cell therapy, especially that of mesenchymal origin.

Indeed, novel state-of-the-art therapeutic approaches for such disorders include the use of mesenchymal stem cells (MSCs), multipotent progenitors present in many tissues including bone marrow, dental pulp and periodontal ligament. MSCs of dental origin have high potential for transdifferentiating various tissue specific cells not only for mesenchymal regeneration but also for neuronal and epithelial reconstruction. These MSCs have also potent immunosuppressive properties inhibiting the proliferation and function of pro-inflammatory immune cells. They also modulate the activity of regenerative regulatory cells which is mediated by cell-cell contacts and by secreted factors.

In this review, we attempted to compare the immuno-patomechanisms of neurodegenerative, neurotraumatic and neuroinflammatory diseases with IBD, and described the potential use of MSCs, especially those that can be obtained

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from dental pulp and periodontal ligament. The startegic goal was to provide a common platform for MSC-dependent healing of central and peripheral disorders related to inflammatory degeneration.

NEURONAL DISORDERS AS POTENTIAL TARGETS FOR MSC THERAPY

Alzheimer's Disease

AD is the most prevalent type of neurodegeneration. It is clinically defined as the onset of progressive deficits in memory and cognition [1-3]. The pathology of AD is characterized by the deposition of insoluble β-amyloid peptides in plaques, intracellular neurofibrillary tangles and also the loss of diverse neurons throughout the brain, particularly in basal forebrain, amygdala, hippocampus and cortical area [4, 5]. AD is multifactorial, heterogeneous and not well understood. But age, sex, apolipoprotein E genotype [6] and sequential proteolytic processing of amyloid precursor protein certainly belong to its risk factors [7]. Current treatment for AD usually includes targeting cholinergic and glutamatergic neurotransmission [8, 9], activation of γ-secretase to generate nontoxic β-amyloid fragments and delivering various growth factors into the brain. These treatments may improve the symptoms, but cannot stop or reverse the degeneration and loss of neurons [10, 11]. A possible avenue for slowing down the progression or even reverse it is the interference with ongoing neuronal cell destruction [12, 13]. In this respect novel approaches interfering with inflammatory cellular and molecular interactions are required. Although in the last decade our knowledge about these processes greatly expanded [14, 15], finding the key components and pharmacologically influence them is still challenging.

Parkinson's Disease

PD is the second most prevalent neurodegenerative disorder after AD. This disease affects millions of individuals with increasing incidence worldwide, and is caused by the preferential degeneration of dopaminergic (DA) neurons of the substantia nigra pars compacta. Symptoms include resting tremor, muscle rigidity, bradykinesia, freezing, and postural instability as well as abnormalities in speech, mood, and cognition [16, 17]. Currently available pharmacological tools, including monoamine oxidase and catechol-O-methyl transferase inhibitors, dopamine receptor agonists, amantadine and L-DOPA, as well as various surgical interventions effectively ameliorate clinical symptoms in the early stages of the disease, but they cannot completely stop or reverse the degeneration of DA neurons, and the symptoms eventually become more pronounced by time [17-20]. Furthermore, the available medications have also considerable side effects. Thus, there is an urgent need to find novel drugs targeting DA and other neurotransmitter systems, growth factors and neurotrophic agents to ameliorate both symptoms and disease progression [19, 21]. New therapeutic avenues are offered by application of stem cells and other regulatory cells interfering with the interplay of cellular and molecular factors, thereby inhibiting accompanying inflammatory processes [16, 22].

Traumatic Brain Injury

TBI is an intracranial damage caused either by an external force that impacts the head breaking through the barriers of the brain (a bump, a violent blow or even a blast) or by extreme acceleration-deceleration and rotational forces. It contributes to 30% of deaths related to injury in the United States, and it is responsible for around 50 thousand death toll each year, 300 thousand hospitalizations and more than 1 million emergency treatments [23-25]. Similar ratios apply for the European Union as well [26]. Depending on the severity, TBI may lead to dizziness, headache, loss of consciousness, bruising, bleeding or even death, and it can be classified as mild, moderate and severe, according to Glasgow Coma Scale scores 3-8, 9-12 and 13-15, respectively [23-25]. Symptoms and neurological deficit caused by TBI may last temporarily, for days, weeks or even for lifetime [23, 27].

TBI consists of two phases. The primary injury is caused by the mechanical damage of neurons, axons, glia and blood vessels, leading to direct neural cell loss, which is followed by a secondary response of multiple biochemical events with various time frames. This secondary damage is characterized by excitotoxicity, oxidative stress, disturbed calcium homeostasis, blood–brain barrier disruption, mitochondrial dysfunction and inflammation, and leads to further neuronal damage mainly in the injury site and near-by tissue [23-25], although neuro-degeneration in brain areas located far from the primary impact has also been reported [28].

Neuroinflammation plays a pivotal role in the pathomechanism of TBI [28-30]. It involves various immune cells, microglia, cytokines, chemokines and other inflammatory mediators. After the primary injury, an endogenous inflammatory response is activated to defend the injury site from pathogens and to repair the damage. Invading neutrophils, monocytes and lymphocytes secrete prostaglandins, pro-inflammatory cytokines, and other inflammatory mediators [31]. The activation of microglia induces both beneficial and detrimental effects. These cells react to acute injury within a few hours, proliferate and migrate towards the site of injury to form a barrier between the damaged and healthy tissue [32]. But their excessive activation leads to increased production of numerous proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, IL-1β, IL-6 and IL-12, as well as to the release of other neurotoxic substances, including nitric oxide (NO) and superoxide free radicals [32, 33]. In addition, activated microglia increase the expression of major histocompatibility complex class II molecules [34], which is also directly correlated to neurodegeneration. However, it is important to note that although activated microglia often act as a major contributor in the inflammatory response, they may promote the opposite effect under appropriate conditions [35]. When exposed to IL-4 or IL-13, microglia can polarize into M2 (or alternatively activated) phenotype (in contrast to the classically activated M1 microglia), and suppress inflammation by reducing the production of proinflammatory cytokines and increasing anti-inflammatory ones, such as IL-10 and transforming growth factor (TGF)-β [32]. All these processes are supposed to be controlled not only by the immune system, but also by an immuno-neuro-stem cell interplay [36].

Spinal Cord Injury

SCI induces motor and sensory deficits impairing the functional activity of the spinal cord, and significantly affects expectancy and quality of life of exposed individuals. The estimated annual incidence of SCI is 2-4 cases per hundred thousand persons [37]. SCI, just like TBI, is followed by primary and secondary injury responses. Primary injury is due to the direct mechanical damage on axons, neuronal cells and blood vessels, while secondary injury is a response to the primary one [38, 39]. It involves extensive chemokine and cytokine liberation and disturbed blood flow, breakdown of the blood-brain barrier, apoptosis, excitotoxicity and production of free radicals [38, 39]. The neuroinflammatory process is very similar to that described above for TBI [40]. Besides surgical interventions, current treatments aim to prevent secondary injuries, promoting regeneration and replacing destroyed spinal cord tissue [40].

Multiple Sclerosis

MS is an immune-related neurodegenerative disorder of the CNS, affecting over 1.3 million people worldwide. It is characterized by the progressive demyelination of nerves in the brain and spinal cord [41, 42]. MS originates from blood-brain barrier disintegrity [43]. Histologically it shows lymphocyte infiltration, loss of oligodendrocytes, demyelination and widespread axonal damage [44, 45]. The consequence is the loss of neurological function with symptoms including pain, muscle spasms, loss of sensation and coordination, impaired vision and emotional distress. Current treatments for MS include the administration of interferon beta, glatiramer acetate, mitoxantrone [46], or dimethyl fumarate [47] but there is no real medical cure for MS for the time being.

During the course of MS, myelin-reactive $CD4^+$ T cells, which secrete interferons and interleukins, play an important role [48]. The best current animal model for MS is experimental autoimmune encephalomyelitis (EAE) [49]. In EAE mice are immunized to induce an immune response to CNS associated antigens. EAE can also be induced by activated myelin-specific $CD4^+$ T cell administration. EAE can follow distinct clinical courses depending upon the mouse strain used and the specific antigen against which the immune response is raised, each reflecting different aspects of MS in humans [49].

INFLAMMATORY BOWEL DISEASE AS POTENTIAL TARGET FOR MSC THERAPY

To eliminate pathogenic bacteria while tolerating harmless commensals, the host immune system must maintain a balance between inflammation and tolerance in the gastrointestinal tract. Disruption of this balance may cause a chronic inflammatory condition that ultimately damages the host tissues in the gut leading to IBD in the colon. Multiple factors are involved in the development of IBD but a common denominator is an initial microbial trigger, followed by an inappropriate polarization of both innate and adaptive immune mechanisms toward an inflammatory phenotype and the down-modulation of regulatory immune mechanisms [50].

IBD, an umbrella term for both Crohn's disease (CD) and ulcerative colitis (UC), encompasses chronic inflammatory disorders of the gastrointestinal tract affecting 2.2 million people in Europe and 1.4 million people in the USA [51]. The chronic inflammation of the gut causes a wide range of clinical symptoms, including nausea, diarrhoea, abdominal pain/discomfort and bloating, even with absorption problems [52]. The course of the disease is intermittent with acute relapses. The chronic inflamed state of the gut may result in fibrosing strictures, fistulas and increased risk of malignancies [51, 53]. The high prevalence of IBDs (~ 0.4 % worldwide) [54] and the costs of the long-term treatment of the patients place a significant burden on the healthcare system: the expenses exceed 1.7 billion dollars per year in the United States [55], and are in similar range in European countries.

Immunopathomechanism of Inflammatory Bowel Disease

The exact immunopathomechanism of IBD is unknown, but it is believed to result from an inappropriate immune response of the intestinal immune system to commensal bacteria and other luminal antigens [56] since the immune system falsely recognizes commensals as pathogens. Complex interactions between genetic, bacterial, and immunological factors are thought to contribute to this process [53, 57-59]. Certainly, an important element in the development of IBD is the barrier disruption leading to a change in the intestinal flora and a consequent aberrant activation of the mucosal immune system [60, 61]. In both CD and UC, isolated diseased intestinal epithelial cells activate CD4+ T cells *in vitro* [62] suggesting that non-immune cells are also able to contribute directly to the inappropriate immune behavior. The resulting inflammation is strongly dependent on CD4+ T helper cells in experimental animals [63]. CD is driven by increased Th1 and Th17 responses, with associated cytokines interferon (IFN)-γ, IL-12, IL-17 and IL-18 [64-66] UC is accompanied by a similar but not identical phenomenon: it is associated with a T cell profile skewed toward Th2 polarization compared to CD and higher mucosal levels of IL-13 [60, 65]. Thus, although T cell dysfunction is not the initiating factor in IBD [67], misregulated Th cell responses seem to play a central role in the progress of the chronic inflammatory process [68].

Different *macrophage* populations play distinct roles in the pathogenesis of IBD. In the lamina propria of healthy mouse intestine, CX3CR1+ macrophages were shown to express anti-inflammatory molecules such as IL-10 and to induce differentiation of Foxp3+ regulatory T (Treg) cells [69, 70]. On the other hand, lamina propria CD11b+ dendritic cells, which promote the differentiation of Th17 cells by increasing IL-17 production [69] were also identified. IL-17 production was suppressed by CX3CR1+ macrophages. Importantly, the existence of distinct macrophage populations has been shown under resting conditions and during inflammation in mouse colon [71]. In normal mice, a large number of F4/80+ macrophages were detected in colon lamina propria, expressing negligible amounts of TNF-α, negative for TLR2 and CCR2 but expressing high levels of CX3CR1 [71]. In ulcerative colitis F4/80+ macrophages express high levels of TLR2, CX3CR1, CCR2 and TNF-α [71]. The presence of two distinct macrophage populations has been shown in human intestine as well. Resident intestinal macrophages were negative for CD14 and produced no

inflammatory cytokines [72]. Another inflammatory macrophage subset was also identified from the intestine of CD patients [73]. These macrophages were positive for the CD14 bacterial LPS co-receptor and produced increased amounts of the proinflammatory cytokines such as IL-23, TNF-α and IL-6 compared to CD14- intestinal macrophages isolated either from healthy subjects or from UC patients [73]. Taken together, the above findings suggest that different macrophage populations exist in the intestine, each having a specific role either in maintaining immune tolerance in health or in perpetuating inflammation in IBD.

Dendritic cells (DC) are the key regulators of immunity against pathogens and tolerance toward commensals and therefore play important roles in intestinal immune homeostasis [74]. In healthy intestine DCs drive the differentiation of naive T cells into regulatory rather than effector T cells [75]. Conversely, an increased number of mature DCs was observed compared to controls in inflamed human colon mucosa [76]. Accordingly, two different populations of DCs have been identified in intestinal lamina propria that mediate either defense or tolerance [74]. One derives from common DC precursors *via* pre-classical dendritic cells and displays a CD103+ CX3CR1- phenotype [77, 78], while the other, CD14+ CX3CR1+ subset is derived from Ly6C+ circulating monocytes [77, 78]. When DCs were depleted and spontaneous self-reconstitution was allowed, mice developed only mild inflammation after a colitogenic challenge [78]. CD103+ DCs inhibit inflammation by potently inducing Treg cells *via* the production of IL-10, TGF-β and retinoic acid [79]. Others have also shown that CD11b+ CD103+ dendritic cells suppress intestinal inflammation by Treg cell activation [80, 81]. In summary, DCs tip the balance between a tolerogenic and a pro-inflammatory immune response by promoting a regulatory or an effector T cell response, respectively.

Adaptive immunity plays a key role in the development of IBD. The classical view held that the intestinal mucosa of patients with CD was dominated by Th1 cells, whereas Th2 cells were dominant in UC lesions [82]. However, certain characteristics of CD and UC were hard to explain based solely on the Th1/Th2 paradigm, and in the last years the involvement of Th17 cells also became evident in IBD both in humans and in animal models. Elevated numbers of Th17 cells are observed in the mucosa of both CD and UC patients compared to normal mucosa [83, 84] and IL-17 is upregulated [83, 84]. Furthermore, IL-17 receptor knockout mice are protected against experimental IBD [85]. The above results underline the role of Th17 cells and IL-17 signaling in IBD. In addition, IL-23, a key cytokine in Th17 development, was also shown to drive innate and T cell mediated intestinal inflammation [86, 87].

Regulatory T cells have been shown to be potent suppressors of intestinal inflammation. The cotransfer of natural Treg (nTreg) cells with naive CD4+ T cells prevents the development of colitis [88]. Moreover, nTregs can also suppress innate intestinal inflammation [89]. The mechanisms by which Treg cells suppress inflammation in the intestine are not entirely clear, but involve the immunoregulatory cytokines TGF-β and IL-10, and the co-stimulatory molecule CTLA-4 [90]. TGF-β inhibits immune responses by several mechanisms: inhibition of antigen-induced activation, proliferation and differentiation of T cells, inhibition of DC maturation and thus favoring the induction of Treg cells, and inhibiting the function of activated macrophages [91]. TGF-β is an important but not the solely factor for the Treg-mediated prevention of colitis [92, 93]. IL-10 has been shown to suppress inflammatory responses in both innate and adaptive models of intestinal inflammation [89, 94]. The role of CTLA-4 in nTreg function is not fully understood [90], but a CTLA-4 agonist has been shown to induce indoleamine 2,3-dioxygenase (IDO) in DCs [95], and IDO expression by antigen presenting cells inhibits T cell proliferation and promotes tolerance [96]. Furthermore, CTLA-4 promotes Foxp3 induction and Treg accumulation in the intestinal lamina propria [97].

STEM CELL THERAPY FOR INFLAMMATORY DISEASES

Potential Stem Cell Sources for Tissue Reconstruction

Stem cells by definition have capacity for unlimited self-renewal and ability to form differentiated cells. They can be classified into totipotent, pluripotent, multipotent and unipotent types by their developmental and differentiation potential or into embryonic, fetal, postnatal (also called adult) and induced stem cell categories by their origin. Embryonic stem cells (ESC) received great attention due to their pluripotency. Recent animal experiments provided evidence that ESC derivatives may provide functional cell replacements in various diseases such as PD [98], and clinical trials are currently in progress utilizing human ESC (hESC) based therapy for macular degeneration and SCI [99]. However, ethical and legal concerns also arise in conjunction with their application. Additionally, transplanted ESCs may induce immune response [100-102] and form teratomas *in vivo* [103]. Reprogramming of mature somatic cells to acquire ESC like characteristics is an alternative idea to avoid most concerns about ESCs. These induced pluripotent stem cells (iPSC) may be derived from the patient's own tissue, bypassing most immunological and ethical problems associated with classical ESCs. Yamanaka received Nobel prize for inventing retroviral vector enforced expression of four key transcription factors, Oct4, Sox2, Klf4 and c-Myc to reprogram mouse fibroblasts to pluripotency and achieving similar developmental capability as ESCs [104]. Since retroviruses may induce cancer [105-107], the technology was further modified to produce iPSCs without any stable genomic modification of the target cells in both mouse [108, 109] and human [110, 111] models. Unquestionably, the fundamental reprogramming of postnatal cells has a great potential, but there are important problems to solve as well. The nature of the reprogramming process remains obscure, and the developmental potential of iPSCs derived by different methods from different tissues is unknown as yet [112]. Therefore, alternative cell sources for stem cell applications also have to be considered.

At present the most promising candidates among adult stem cells for clinical applications are the MSCs, a class of multipotent cells originally identified in bone marrow [113, 114]. Their high plasticity, in addition to their presence even in adult humans validate them attractive candidates for

therapeutic use. Yet, standardized, reliable protocols are still to be developed for differentiating these cells into target tissues in large quantities [115, 116].

Mesenchymal Stem Cells

Since MSCs have been discovered in bone marrow, a number of other tissues such as brain, skin, skeletal muscle and the gastrointestinal tract have been shown to contain similar cell populations [117-119] including oral tissues [120]. It has also been demonstrated that MSCs have the potential to directly differentiate into multiple lineages of mesenchymal origin, including bone, cartilage, fat, connective tissue, smooth muscle and hematopoietic supportive structures [121].

An important selection criterion for MSCs is their plastic adherence and capacity to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro* [122]. These cells express a variety of cell surface marker proteins such as CD73, CD90 and CD105. Additionally, MSCs do not express major histocompatibility complex class II surface molecules, endothelial CD31, and hematopoietic-specific markers CD34, CD45 and CD14 [121, 122]. Isolated MSC cultures are heterogeneous. Various research groups proposed specific cell surface markers to identify MSCs such as STRO1 (stromal precursor antigen 1) [123], GD2 (ganglioside 2) [124], SSEA4 (stage-specific embryonic antigen-4) [125], and CD146 [126], but the optimal combination of selection factors still needs to be identified.

Mesenchymal Stem Cells as Immunomodulators

One of the most intriguing features of MSCs is that they are not only able to facilitate tissue regeneration by differentiating into several cell types, but also able to escape immune recognition and to inhibit immune response. Therefore, MSCs may serve as immunosuppressive agents in inflammatory diseases, and other autoimmune diseases [127, 128]. These immunomodulatory effects of MSCs seem to be achieved by multiple mechanisms inhibiting pro-inflammatory cells and at the same time activating other immune cells that shift the balance toward regeneration.

First of all, MSCs inhibit T cell proliferation in mixed lymphocyte cultures *in vitro* [129-133]. The effect is primarily mediated by soluble factors [127, 134] such as TGF-β [130], hepatocyte growth factor [130], IL-10 [135] and prostaglandin E2 (PGE2) [136]. MSCs also block T cell proliferation by the secretion of IDO [137, 138]. The production of nitric oxide (NO) is also a potential mechanism by which MSCs inhibit T cell proliferation [139]. MSCs can also block pathogenic B cell response [140, 141]. Natural killer (NK) cells are parts of the innate immune system, having antitumor and antiviral effects due to their cytotoxic potential and secretion of pro-inflammatory cytokines such as TNF-α and IFN-γ. They contribute to inflammatory conditions in IBD [142]. MSCs suppress proliferation and secretory activity of NK cells [143, 144].

MSCs also modulate the immune system by acting on antigen presenting cells. The differentiation of CD34+ hematopoietic stem cells into DCs was prevented by MSCs [145]. MSCs also inhibit the differentiation of CD14+ human monocytes into dendritic cells and reduce their IL-12 secretion [146]. Another study essentially confirmed these results, reporting in addition that the inhibition of DC maturation but not differentiation was dependent on soluble factors [147]. MSCs alter the cytokine secretion profile of DCs as well, converting them into a regulatory phenotype [135, 136]. In an experimental cecal ligation and puncture sepsis model, PGE2 secreted by exogenously administered MSCs was reported to reprogram macrophages to produce IL-10, a potent anti-inflammatory cytokine, thereby sparing mice from dying of sepsis [148]. These findings show that MSCs suppress the differentiation and activation of antigen presenting cells and shift their development toward a regulatory phenotype.

MSCs may modulate the induction of CD4+ CD25+ Treg cells, too [136, 149]. MSCs prevent diabetes mellitus in NOD mice *via* the induction of IL-10 producing Treg cells [150]. The induction of CD4+ CD25+ FoxP3+ Treg cells by MSCs results in increased allograft tolerance in kidney transplantation [151]. Other studies have also shown that the effects of MSCs in autoimmune diseases at least partly due to the generation of antigen-specific CD4+ CD25+ FoxP3+ Treg cells [152, 153]. MSCs inhibit the differentiation and maturation of monocyte-derived dendritic cells and augment the generation of Treg cells [154].

The immunosuppressive effects of MSCs are partly mediated by cell–cell contact [154], however, soluble factors such as PGE2 and TGF-β1 also play a role [155]. Human gingiva-derived MSCs suppress peripheral blood lymphocyte proliferation by inducing IL-10, IDO, inducible NO synthase (iNOS) and cyclooxygenase 2 (COX-2) in experimental colitis [156]. Another study showed that the immuno-suppressive effect of MSCs is mediated by the secretion of galectin-3, a protein known to modulate T cell proliferation, gene expression, cell adhesion and migration [157].

Activation and Polarization of MSCs

Under resting conditions MSCs possess antiapoptotic and supporting properties toward different cells types such as hematopoietic stem cells, T cells, B cell precursors, plasma cells and neoplastic cells. Also, MSCs may act as antigen presenting and pro-inflammatory cells. Thus, the immuno-modulatory activity is not constitutively exerted by MSCs, but depends on a process of 'licensing' to be acquired. This involves a functional polarization depending on the cytokine milieu and toll-like receptor stimulation. Initial priming of human MSCs with either IFN-α or IFN-γ synergizes with downstream TLR3 or TLR4 stimulation to enhance the production of pro-inflammatory cytokines. The concentration of inflammatory cytokines has also been postulated to regulate MSC polarization. IFN-γ, IL-1 and TNF-α are key elements of the activatory milieu. Their induction of iNOS and NO production have been shown to be an effector mechanism inhibiting T cell proliferation [158].

As the proper activation of the MSCs is crucial to achieve the anti-inflammatory phenotype, the failure of some MSC-based protocols for immune modulation in animal models and in human clinical trials may be explained by either lack of a proper licensing by inflammatory microenvironment or incorrect timing in MSC administration

[159]. Thus, optimization of MSC administration for immune-regulating purposes is required to maximize their beneficial effects.

MSCS FOR HEALING AND REGENERATION OF NEURONAL DISEASES

Alzheimer's Disease as MSC Target

The potentially beneficial mechanisms of MSCs in the treatment of AD are not well understood, but certainly multifactorial. MSC-derived neurons have the capability to integrate into the existing neural networks of the host brain [160]. The release of neurotrophic and immunomodulatory factors from MSCs may improve the host environment [22]. MSC-based therapy may have neuroprotective effect by secretion of neurotrophic factors such as NGF and brain-derived neurotrophic factor (BDNF) [161-164]. Since AD is accompanied by chronic inflammation, MSCs exert anti-inflammatory effects by reducing pro-inflammatory cytokine release and upregulating expression of anti-inflammatory factors including IL-10 [165-167]. Abnormal accumulation of β-amyloid peptide is regarded to be an important pathological sign in AD, and its inhibition has been implied to delay AD progression. Engrafted MSCs have been demonstrated to eliminate deposited β-amyloid plaques brain through differentiation into microglia or recruitment of activated endogenous microglia in AD [12, 168].

Microglia cells exist in a quiescent state, but they prevent and/or clear β-amyloid peptide deposition when activated [169, 170]. MSCs activate and induce migration of microglia when exposed to β-amyloid peptide *in vivo* [171]. An alternative activation of microglia in AD mice is associated with elevated chemokine expression by MSCs [168]. MSCs can induce a neuroprotective effect in harmful microglia by increasing expression and release of CX3CR1, thus contributing to their beneficial effects [172, 173]. MSCs themselves can also differentiate into microglia and eliminate β-amyloid peptide deposition [166]. Additionally, MSCs could turn on neuroregeneration inducing neurogenesis, neuroplasticity, and neurorestoration in AD [1, 174-176].

Parkinson's Disease as MSC Target

Several preclinical studies suggest that MSCs may have a great therapeutic value in PD [177, 178]. Various types of MSCs, including bone marrow-derived MSCs [179], adipocyte- [180] and umbilical cord-derived SCs [181] were shown to induce neuroprotection both *in vitro* and *in vivo*. Moreover, this neuroprotection can be achieved not only by engrafting MSCs directly into the striatum [179], but also by applying them *via* other routes, such as intranasally [182] or intravenously [183].

In the last years several mechanisms were implicated in the regenerative effect of MSCs in PD [22]. Although transdifferentiation of MSCs into DA neurons or their fusion with host neurons may also contribute to their beneficial effect [184, 185], several lines of evidence indicate that the neurological improvement observed after MSC-treatment is mainly due to secretion of bioactive factors [178]. MSCs secrete a wide array of growth factors; many of which, such as BDNF, glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF), fibroblast growth factor 20 (FGF20) and basic fibroblast growth factor (bFGF) elicit potent trophic and neuroprotective effects on nigrostriatal DA neurons [180, 186]. MSCs transplanted into the striatum of 6-OHDA-lesioned rats differentiated toward an astroglial phenotype and increased GDNF expression, which resulted in neuroprotection [179]. There is evidence that neurotrophic factors released by grafted MSCs not only promote neuronal regeneration, but also induce proliferation and differentiation of endogenous neural stem cells, which thereafter release various endogenous neurotrophins [187]. Furthermore, MSCs secrete a variety of neuroregulatory molecules, cytokines and chemokines, which also promote neuronal survival and differentiation [187, 188].

Neuroinflammation has been recognized recently as an important contributor to the pathogenesis of PD. In fact, anti-inflammatory drugs are emerging as novel therapeutic tools to suppress neuronal degeneration [189, 190]. Therefore, it is of interest that MSCs are able to induce immunomodulatory and anti-inflammatory actions. For instance, MSC treatment has been demonstrated to decrease LPS-induced microglial activation and TNF-α and iNOS production, resulting in a significant reduction of DA neuronal loss [191]. Other mouse studies showed that MSCs promote the recovery of blood-brain barrier integrity and protected DA neurons from pharmacological toxicity through decreased microglial activation [192]. Thus, these studies underline the importance of MSC-induced immunomodulatory and anti-inflammatory effects in treatments for PD.

Traumatic Brain Injury as MSC Target

As depicted above, several biochemical events take part in the secondary phase of TBI, and considerable effort has been invested to find novel approaches to inhibit these processes and reduce the neuronal damage. A large number of preclinical studies suggest that various stem cells, including MSCs may promote the regeneration in TBI [24]. Similar to other neurodegenerative diseases, the beneficial effect of MSCs in TBI was originally attributed to their ability to differentiate into neurons and replace the damaged cells [193, 194]. However, currently it is believed that secretion of cytokines, chemokines and growth factors, inhibition of inflammation and enhancement of endogenous neurogenesis and angiogenesis are equally if not more important factors in the therapeutic effect of stem cells [36, 195].

MSCs are able to influence several processes during the secondary phase of tissue response during the course of TBI. They effectively inhibit neuroinflammation due to their potent immunomodulatory properties. Stereotactic or intravenous injection of MSCs was shown to decrease the level of various pro-inflammatory cytokines, such as IL-1β, IL-6, IL-17, IFN-γ or TNF-α both in the serum and brain after cerebral injury [36, 195]. MSCs migrate to the injury site and modulate the inflammatory response activating T lymphocytes, neutrophils, and microglial cells. The immunomodulatory effect of MSCs is at least partly due to the secretion of the TNF-α-stimulated gene/protein 6 (TSG-6), which possess potent anti-inflammatory action by

suppressing the NF-κB signaling pathway [36, 196] and inactivating the pro-inflammatory hyaluronan [197]. Additionally, MSCs reduce the production of chemokines CXCL2 (or MIP-2) and CCL2 (or MCP-1) secreted by microglia and neurons. These are important chemoattractants for various immune cells and play significant role in the secondary brain damage [36].

Besides their direct immunomodulatory properties, MSCs have additional beneficial effects in TBI. Intravenous administration of MSCs significantly improved blood-brain barrier function by reducing endothelial permeability, increasing VE-cadherin expression and VE-cadherin/β-catenin interaction [198]. Furthermore, hMSC-conditioned medium reduced superoxide production in an TBI model *in vitro*, suggesting that MSCs are also able to regulate the oxidative stress [199]. These studies clearly demonstrate that MSC-treatment induces numerous favorable effects in TBI and effectively reduces the secondary damage.

Spinal Cord Injury as MSC Target

Just like in other neuronal disorders, MSCs could be beneficial in SCI primarily because of their anti-inflammatory, immunomodulatory [200] and neuroprotective [201] effects. Moreover, the trophic effect of MSC-secreting pro-survival factors such as insulin-like growth factor (IGF), BDNF, vascular endothelial growth factor (VEGF), granulocyte-macrophage colony stimulating factor (GMCSF), FGF2 and TGF-β [202-206] could be of importance. Indeed, the healing actions of MSCs were confirmed by several investigations in SCI. The effects were attributed to secretion of neurotrophic factors [207, 208] and anti-inflammatory cytokines [209-211]. Furthermore, MSCs promoted axonal growth and sprouting in multiple species [212, 213].

Despite the large number of studies, very little is known about the exact mechanisms by which MSCs ameliorate SCI [214]. A recent study has shown that MSCs could alleviate spinal cord inflammation by weakening TLR4-mediated signaling pathways and reducing tissue levels of IL-1β and TNF-α [215]. In addition, MSCs exhibit marked anti-proliferative and anti-apoptotic effects leading to the reduction of inflammation in the site of SCI [209, 216-220]. Importantly, following SCI, MSC grafts modify the inflammatory environment by shifting macrophages from pro-inflammatory to anti-inflammatory phenotype, sparing axons and myelin [221]. MSCs also provide a permissive environment by stimulating angiogenesis [222]. All these factors contribute to healing, but probably the synergism of the above mechanisms is even more important.

Multiple Sclerosis as MSC Target

As described above, EAE is the best known and most commonly used model for MS showing both immunological and clinical manifestations of the human disease [45]. Transplantation of MSCs into EAE mice resulted in rapid and sustained functional recovery due to the reduced number of inflammatory myelin-specific Th1 cells and astrocytes as well as an increased number of inflammatory-inhibiting Th2 cells, oligodendrocytes and neurons. The effect was strong only if MSCs were administered prior the onset of the disease but not afterwards [223]. Human MSCs were similarly effective in EAE [224] suppressing the disease. The mechanisms of the MSC-mediated immunosuppression in EAE are not well understood. The reduction of inflammatory cytokine secreting T cells [225], and diminished T cell response to antigenic stimulation have been observed [223]. MSCs appear to mediate immune suppression at least partly by CCL2 chemokine [225] since $CCL2^{-/-}$ MSCs are unable to suppress disease [225]. These data along with other observations demonstrate that a defective MSC function may be important in the pathogenesis of EAE, because MSCs deriving from mice with ongoing disease were unable to suppress disease upon transfer to autologous recipients [42, 226]. Human clinical trials have also reported promising preliminary results for the use of MSCs. Besides beneficial clinical measures, MSCs increased the proportion of CD4+/CD25+ Treg cells, whereas the proliferative responses of lymphocytes decreased [227-229].

INFLAMMATORY BOWEL DISEASE AS MSC TARGET

In the past years a several animal studies were conducted to analyze the effect of various types of MSCs in colitis models; Table **1** provides a non-exhaustive list. MSCs isolated from human or murine adipose tissue, for instance, were shown to alleviate colonic inflammation by decreasing the level of inflammatory cytokines and chemokines, increasing IL-10 levels, inhibiting Th1 cell expansion and inducing Treg cells both in trinitrobenzene sulfonic acid (TNBS)-induced colitis [152] and in dextran sulfate sodium (DSS)-induced colitis [153] in mice. In rats, topical application of MSCs was reported to accelerate healing in TNBS-induced colitis, an effect thought to be mediated by increased production of TGF-β1 and VEGF [230]. In a DSS-induced rat experimental colitis model, intravenously administered MSCs reduced clinical signs of colitis and the expression of inflammatory cytokines in the rectum and accumulated within the lamina propria in inflamed regions [231].

Clinical trials suggest that MSCs may be a promising therapeutic options in IBD. In a phase I trial, the intravenous use of expanded autologous MSCs was reported to be safe in the treatment of refractory CD, even though only a third of the patients showed favorable clinical response [232]. Allogenic MSCs administered intravenously to 10 CD and 39 UC patients, however, resulted a beneficial effect on the clinical and morphological presentation of the inflammatory process in 80% of the patients [233]. Local/intrafistular use of MSCs was also shown to be effective in fistulizing CD: in a human phase II clinical trial, local injection of ASCs dramatically increased the healing of perianal fistulas both in CD and non-Crohn's patients [234]. Likewise, intrafistular autologous MSC injections resulted in the closure of fistula tracks (70% complete, 30% incomplete), rectal mucosal healing and increased numbers of mucosal and circulating Treg cells with no side effects in CD patients [235].

MSCs OF DENTAL ORIGIN – NEW SOURCES FOR REGENERATIVE MEDICINE

Stem cells of dental origin, such as those isolated from the dental pulp (DPSC), exhibit mesenchymal stem cell

Table 1. Examples for the protective effects of MSCs in animal colitis models.

Animal	Colitis Model	Type of Stem Cells	Amount, Route and Time of Appl.	*In Vivo* Effects	Refs.
Sprague-Dawley rat	TNBS	rat BMSC	1 x 10^7 topically (submucosal injection) and i.v., immediately after TNBS	- i.v. no effect, accumulation in lungs - topically protection, acceleration of healing, expression of VEGF and TGF-β1	Hayashi *et al*., 2008 [230]
Lewis rat	DSS	rat BMSC	2 x 10^4/g i.v. on day 2	- no effect on inductive phase, modest promotion of recovery - most growth factors and cytokines remained unchanged, but TGFα was increased and Notch signaling was inhibited	Tanaka *et al*., 2011 [272]
C57BL/6J mouse	DSS	human BMSC and GMSC	2 x 10^6 i.p., on day 2	- amelioration of colitis, suppression of $CD4^+$ T lymphocyte infiltration, reduction of pro-inflammatory cytokines IFN-γ, IL-6 and IL-17, elevation of IL-10	Zhang *et al*., 2009 [156]
Balb/c mouse	TNBS	human and mouse ASC	$1x10^5$ – 10^6 i.p., 12 h after TNBS (hASCs and mASCs) and 10^6 i.p., 6 and 7 days after TNBS (hASCs)	- inhibition of colitis development, partial reversal of already established colitis, decreased MPO activity, reduction of pro-inflammatory cytokines (TNF-α, IFN- γ , IL-6, IL-1β, IL-12) and chemokines (RANTES and macrophage inhibitory protein 2), elevation of IL-10	Gonzalez *et al*., 2009 [152]
C57BL/6 mouse	DSS	human and mouse ASC	$1x10^5$ – $5x10^6$ i.p, on day 2, or in the case of cyclic DSS administration on day 7 of each cycle	- amelioration of colitis, decreased MPO activity, reduction of pro-inflammatory cytokines (TNF-α, IFN- γ , IL-6, IL-1β, IL-12) and chemokines (RANTES and macrophage inhibitory protein 2), elevation of IL-10	Gonzalez-Rey *et al*., 2009 [153]
C57BL/6J Ico mouse Balb/c mouse	DSS TNBS	untreated and IFN- γ-prestimulated human and mouse BMSC	$0.5x10^6$ i.p, on day 0 $1x10^6$ i.p, 6 h after TNBS	- IFN- γ-prestimulated cells, but not untreated cells induced protection, decreased serum amyloid A levels, reduced TNF-α, IL-6 and IL-17A, increased the level of IL-10	Duijvestein *et al*., 2011 [268]
Balb/c mouse	DSS	mouse BMSC	$1x10^6$ i.v, on days 2, 5 and 8	- alleviation of colitis, reduction of pro-inflammatory cytokines TNF-α and IL-1β	He *et al*., 2012 [270]
C57BL/6J mouse	DSS	rat DPSC	$1x10^5$/10g i.v, on day 3	- protection from colitis *via* Fas ligand-induced T cell apoptosis	Zhao *et al*., 2012 [251]
Wistar rat	TNBS	rat ASC and BMSC	$2x10^6$ i.p., 4 days after TNBS	- i.p., but not i.v. injected stem cells migrated to the inflamed colon - alleviation of colitis, reduction of epithelial apoptosis and pro-inflammatory cytokine production (TNF-α, IL-1β), elevation of IL-10	Castelo-Branco *et al*., 2012 [278]
Balb/c mouse C57BL/6 mouse	TNBS DSS	mouse ASC and ASC-induced regulatory macrophages	$1x10^6$ i.p, immediately after TNBS, or in the case of chronic colitis on days 8 and 16 $1x10^6$ i.p, on day 2, or in the case of chronic colitis on days 4 and 14	- inhibition of colitis development and progression, decreased MPO activity, reduction of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and chemokines (RANTES)	Anderson *et al*., 2013 [279]
C57BL/6 mouse	DSS	mouse ASC	$1x10^6$ i.v or i.p., on days 2 and 5	- i.p. no effect - amelioration of colitis only in the case of i.v. administration	Goncalves *et al*., 2014 [269]
Balb/c mouse	DSS	mouse BMSC	$2.5x10^6$ i.v, on day 7	- accelerated recovery, improved epithelial barrier function *via* restoration of E-cadherin expression, reduction of oxidative stress	Sun *et al*., 2015 [280]
C57BL/6 mouse	DSS	untreated and IFN- γ-overexpressed human UCSC	$1x10^6$ i.v., on day 2	- IFN- γ-overexpressed stem cells ameliorated colitis, reduced the number of Th1/Th17 cells and increased that of Treg/Th2 cells, decreased TNF-α, IL-6 and IL-1β, upregulated indoleamine 2, 3-dioxygenase expression	Chen *et al*., 2015 [281]

Abbreviations for MSCs by origin: BMSC – bone marrow-derived mesenchymal stem cell, GMSC – gingival mesenchymal stem cell, ASC – adipose tissue-derived mesenchymal stem cell, DPSC – dental pulp mesenchymal stem cell, UCSC – umbilical cord-derived stem cell.

characteristics [120, 236, 237]. These cells have multiple differentiation potential towards osteogenic and odontodenic directions as well as neurogenic, adipogenic and chondrogenic lineages [120, 236-241]. Previous studies provided evidence that not only the human and rat dental pulp stem cell cultures, but also those originating from the periodontal ligament (PDLSC) may serve as MSC sources for regenerative purposes [50, 238, 242].

Potential for MSCs of Dental Origin in the Therapy of Neuronal Diseases and IBD

In addition to their potential for self-renewal and multi-lineage differentiation capacities, dental MSCs have strong anti-inflammatory and immunomodulatory properties comparable to other MSCs [243, 244]. In this respect it is important to note that oral MSCs derive from neural crest cells, whereas bone marrow MSCs originate from the mesoderm. Therefore, some differences in their behavior are predictable [245, 246].

DPSCs were shown to inhibit the proliferation of stimulated T cells [131, 247]. This immunomodulatory activity indicates that DPSCs could be suitable to suppress T cell-mediated graft-versus-host reaction in bone marrow transplantation [133]. Additionally, DPSCs inhibit peripheral blood mononuclear cells (PBMCs) proliferation induced either by mitogenic signals or allogeneic mixed lymphocytes. This effect is most likely mediated at least in part by TGF-β, acting on its receptors on PBMCs [248]. Toll-like receptors may be able to trigger the immunosuppression by DPSCs through the increased expression of TGF-β and IL-6 [249]. Indeed, immature human DPSCs were shown to induce immunosuppression in a canine model of Duchenne muscular dystrophy leading to the relief of symptoms [250]. Recent investigations have demonstrated that human and rat DPSCs are able to induce apoptosis of activated T cells *in vitro* [251]. In addition, in DSS-induced colitis in mice, rat DPSCs exhibited a very strong ameliorating effect when infused systemically [251].

The DSS-induced induced colitis in mouse is a well-established model of ulcerative colitis. Although the exact mechanism is not known, it is likely that the mucosal damage results from the complex maladaptive immune response triggered by the proinflammatory content of the bowel disseminating through the DSS caused epithelial barrier destruction [156, 252, 253]. The transmembrane protein Fas ligand (FasL) plays an important role in inducing the "Fas/FasL" apoptotic pathway. FasL silencing by siRNA in DPSCs resulted in the reduction of T cell apoptosis in cell culture and also strongly inhibited the deteriorating effect of DSS in the mouse colon [251]. The therapeutic mechanism may be related to the reduced colonic infiltration of inflammatory cells and down-regulation of inflammatory cytokines [251]. Other mechanisms may involve increased infiltration of Treg cells and the expression of anti-inflammatory cytokine IL-10 at the colonic sites [156]. Interestingly, FasL knockdown in rat DPSCs resulted in a reduced capacity to ameliorate colitis phenotypes, indicating that FasL is required for DPSC-mediated immunoregulation. Moreover, *in vitro* co-culture assays demonstrated that DPSCs induced apoptosis of Th17 but not Treg cells, suggesting that such FasL-mediated apoptosis was specific for T-helper cells. This finding is consistent with previous observations using bone marrow MSCs [252]. Furthermore, FasL knockdown did not affect the multipotent differentiation capacity of DPSCs, suggesting that the role of FasL may be limited to controlling the interaction between DPSCs and immune cells [251].

In co-culture studies, PDLSCs suppressed the proliferation of PBMCs without promoting their apoptosis [254]. In another study, Wada and colleagues found that PDLSCs, DPSCs and BMSCs induced the production of TGFβ1, hepatocyte growth factor and IDO, which in turn suppressed PBMC proliferation [248]. When PDLSC cell sheets were applied in a minipig periodontitis model *in vivo*, no immunological rejection was observed. Instead, PDLSCs ameliorated the experimental periodontitis in this model by PGE2-dependent manner, suppressing the activation of T cells [255]. The inhibitory effect on T cell proliferation was diminished using PDLSCs isolated from inflamed PDL. It was also shown that activated PBMCs exhibited significantly less induction of CD4+ CD25+ Foxp3+ Treg cells and IL-10 secretion in the presence of PDLSCs from inflamed tissue, than those co-cultured with normal PDLSCs. Furthermore, suppression of Th17 differentiation and IL-17 production were significantly less by these cells than normal PDLSCs [256]. Taken together, these data show that PDLSCs exert their immunomodulatory effects *via* similar mechanisms as BMSCs or DPSCs.

At present, information on the beneficial effects of dental originated MSC on neuronal disorders are scarce, but very promising. Certainly, DPSCs are able to differentiate into neurons *in vitro* when appropriate environment is formed and the right combination of neurodifferentiation agents are applied [238, 240, 257]. These neuro-differentiated cells are able to survive and integrate into the damaged brain [258]. Furthermore, DPSCs were shown to enhance post-stroke functional recovery, probably at least in part through non-neural replacement mechanisms [259]. DPSCs also promoted locomotor recovery after complete transection of the rat spinal cord by activating multiple mechanisms [260]. One of the identified potential mechanisms is the direct induction of endogenous axon guidance, a process which is very important for complex neuronal regeneration [261].

Taken together, MSCs of dental sources represent a high, but a yet not fully explored potential for treating neurodegenerative traumatic, and inflammatory diseases independent whether they appear in the central nervous system, the gut or other organs. However, human therapeutic use requires far more preclinical and clinical investigations.

TREATMENT OF DSS-INDUCED COLITIS WITH hDPSCs IN MICE – OUR OWN EXPERIENCE

To investigate the effect of human DPSCs on IBD, our group used the DSS-induced mouse colitis model. Human DPSCs were obtained from impacted wisdom teeth, the isolation procedure was carried out as previously reported [239, 240]. In brief, DPSCs were cultured in αMEM

supplemented with 10% FBS, 2 mM L-glutamine, 100 U/ml penicillin and 100 µg/ml streptomycin under standard conditions (37 ˚C, 5% CO_2). Cells from early passages (up to P3) were used for experiments.

Acute colitis was induced in 8 weeks old female C57BL/6 mice by adding DSS (3%, molecular weight: 35 000-55 000 Da; TdB Consultancy, Uppsala, Sweden) to the drinking water (tap water) for 7 days (see protocol, Fig. **1A**). The DSS-containing drinking water was made up fresh every second day to avoid bacterial contamination. Food and water were available ad libitum; the consumption of water and food was monitored in all groups. Body weight was measured daily during the course of the treatment. The development of colitis was evaluated by recording disease activity index (DAI) covering general appearance (score: 0-1), stool consistency (score: 0-3) and presence of faecal blood (score: 0-3) summed to a total score ranging 0 to 7 (modified from Reichmann *et al*. [262]). Human DPSCs were injected intravenously at day 3 after colitis induction, at a dose of 1 x 10^5 cells/10 g body weight in 100 µL saline (based on the protocol of Zhao *et al*. [251]). At day 9 after colitis induction mice were sacrificed by decapitation and their whole colon were removed and the reduction of colon length measured to assess colonic inflammation [263]. All experimental procedures were carried out according to ethical guidelines issued by the Ethical Board of Semmelweis University, based on EC Directive 86/609/EEC and were approved by the National Scientific Ethical Committee on Animal Experimentation and permitted by the government (Food Chain Safety and Animal Health Directorate of the Central Agricultural Office, Permit no. PEI/001/1493-4/2015). Data are expressed as means ± S.E.M. Statistical analysis of the data was performed either with one-way ANOVA followed by Bonferroni post-hoc test, or with two-way repeated measures ANOVA in order to compare the time course of disease activity indices and weight losses between different groups. A probability of $p<0.05$ was considered statistically significant.

Beneficial Effect of hDPSCs on DSS-induced Colitis in Mice

Administration of 3% DSS-induced a moderate to severe inflammatory response in the animals, characterized by elevated DAI (significant elevation from day 6, Fig. **1B**),

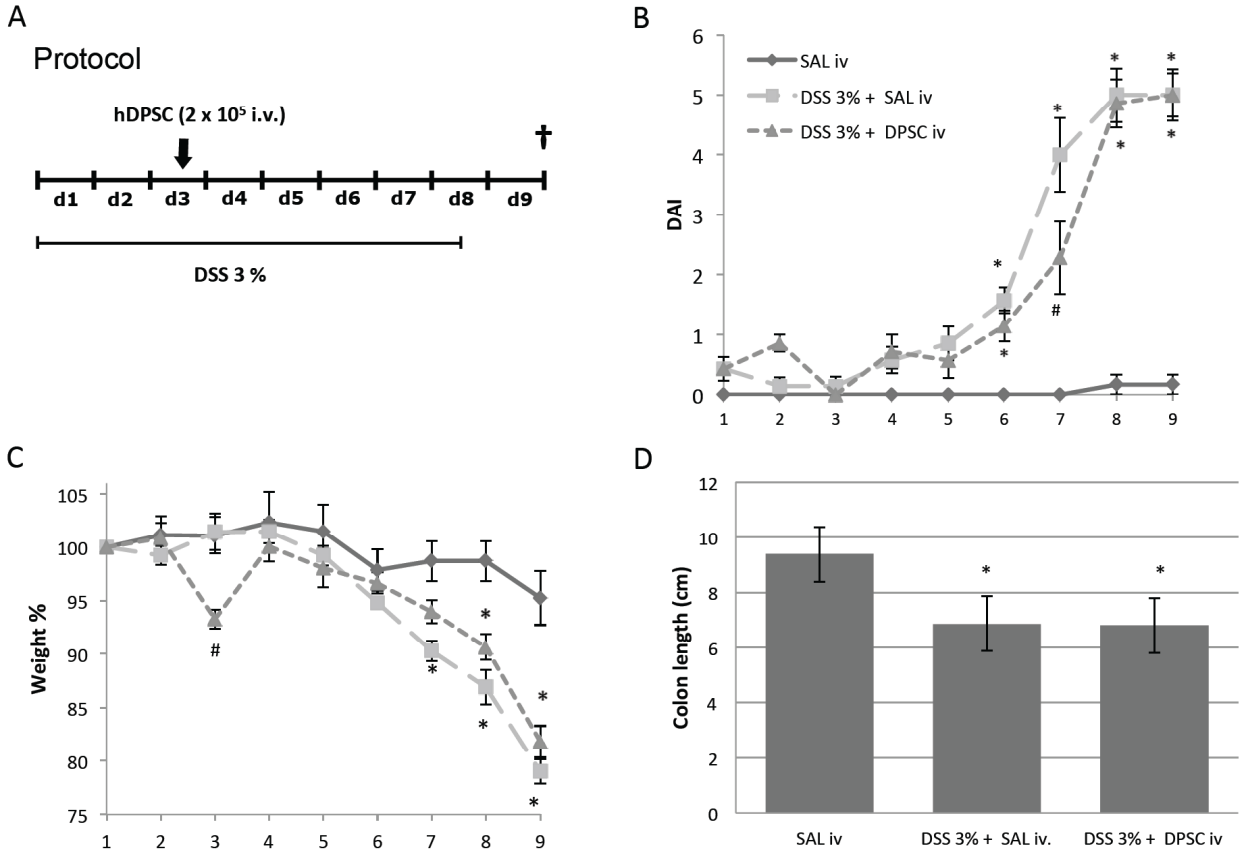

Fig. (1). Effect of intravenously administered human DPSCs on acute experimental colitis in mice. Animals were treated with DSS (dextrane sulfate sodium) for 7 consecutive days, and sacrificed at day 9. DPSCs were administered at day 2 (Fig. **1A**). DSS-induced a moderate to severe colitis resulting in an increased disease activity index (DAI; significant elevation from day 6, Fig. **1B**), marked weight loss (significant from day 7, Fig. **1C**) and shortened colon on day 9 (upon sacrifice) (Fig. **1D**). Treatment with hDPSCs delayed the development of colitis, indicated by a lower DAI value (2.3 ± 0.6 vs. 4.0 ± 0.6, $p<0.001$) and the lack of significant weight loss on day 7. The severity of the colitis, however, did not differ between the saline-treated (SAL) and hDPSC-treated animals at day 9, as comparable DAI values, weight reductions and colon lengths were measured. *$p<0.05$ vs saline-treated (SAL) group, #$p<0.05$ vs saline+DSS-treated group. n=6-7/group.

marked weight loss (significant from day 7, Fig. **1C**) and shortened colon on day 9 (upon sacrifice) (Fig. **1D**). Treatment with hDPSCs considerably delayed the development of colitis, as manifested in lower DAI value (2.3 ± 0.6 vs 4.0 ± 0.6, $p<0.001$) and the lack of significant weight loss on day 7. At the end of the experiment, however, the severity of colitis did not differ between the saline-treated and hDPSC-treated animals, and comparable DAI values, weight reductions and colon lengths were measured.

As described above, Zhao *et al*. reported that systemic infusion of rat DPSCs protected mice from DSS-induced colitis *via* FasL-induced T cell apoptosis [251]. They observed similar FasL-dependent apoptotic effect in the case of human DPSCs *in vitro*, which, together with other studies demonstrating the immunomodulatory effect of hDPSCs [248, 252, 264], foreshadow that these cells are also able to ameliorate colonic inflammation [265]. However, to our best knowledge this issue has not been directly addressed yet. Our results indicate that a single intravenous injection of hDPSCs beneficially alters the development of acute colonic inflammation *in vivo*. On the other hand, the anti-inflammatory action of hDPSCs in our experimental setting was less pronounced than the protective effect of rDPSCs in the study by Zhao and co-investigators [251]. Although hDPSCs delayed the onset of the disease in our experiment, the beneficial effect was not strong enough to alleviate to full-blown symptoms.

The difference between the efficacy of DPSC in our study and in others could be due to a number of factors. First, the severity and course of the inflammation shows considerable variability across different studies, even if mice with similar strain, sex, age, and weight were used. This phenomenon may partly be explained by the different composition of the gut microbiota, resulting from slightly different environmental conditions in the different laboratories. It is well established that differences in the gut microbiota substantially alter the immune responses of the host [266], including the susceptibility of mice to DSS [267] and the microbiota strongly depends on housing conditions and diet [267]. Considering this, it is possible that our mice were more susceptible to DSS, and its damaging effect could not be so effectively abrogated by hDPSCs. This assumption is also supported by the fact that in our experiment DSS-induced weight loss was much more pronounced (3.9 g vs. around 2.5 g on day 9). It is also important that although we used DSS with the same molecular weight (~ 35-55 kDa), it came from a different source, which may also contribute to the observed difference.

It is also important to note that the heterogeneity of MSC preparations originating from different tissue sources, isolated by slightly different protocols and cultivated by similar, but somewhat variable methods may result in different biological activities. Various MSC preparations were successfully applied in the mouse colitis model to alleviate the inflammatory process [156, 251, 268-271], but their relative potency is still unknown. Moreover, several studies reported that MSCs without prestimulation had no or very mild effect on experimental colitis [269, 272, 273] and cytokine inducible functional maturation was needed to earn full anti-inflammatory MSC phenotype [159]. Indeed, pre-stimulation with INF-γ and TNF-α significantly enhanced the protective action of MSCs in murine colitis [268, 274-277]. Accordingly, the efficacy of MSCs may rely on the exogenous and endogenous cytokine levels and on the timing of MSC administration [159].

Our data showing the protective effect of human DPSCs in experimental colitis are in accordance with the available literature about the beneficial effects of other MSCs in this model. Nonetheless, the efficiency of stem cell treatment even in a well-defined disease model could be variable, depending on the preconditioning, timing, administration, species and probably by a number of presently unidentified factors.

CONCLUSIONS

Although Alzheimer's disease, Parkinson's disease, traumatic brain and spinal cord injuries and multiple sclerosis, are classically categorized as rather different diseases of the CNS, recent data indicate that they are all characterized by tissue damage due to an inappropriate inflammatory/immune response. This shows remarkable similarities with the known pathomechanisms of the inflammatory bowel diseases. Conventional pharmacological and surgical therapies are not sufficient to prevent, slow down or stop these processes, or to promote the regeneration of damaged tissue. Since mesenchymal stem cells potentially offer solution for both problems, the treatment of neuronal and gastrointestinal inflammatory diseases with MSCs is an emerging area of great interest. Importantly, MSCs can be obtained from a different of sources including dental tissues. These cells can be expanded to generate a sufficient number of cells for therapeutic purposes *ex vivo*. To our current knowledge, the beneficial effects of MSCs can be mainly accounted for their immunomodulatory and anti-inflammatory effects. Thus, the use of MSCs from different sources (including the dental pulp and the periodontal ligament) represent a very promising approach to treat diseases involving immune-mediated tissue destruction, either in the gastrointestinal or in the central nervous system.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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