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Myeloid cell-based therapies in neurological disorders: How far have we come?☆

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ABSTRACT

The pathogenesis of neurological disorders such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) is multifactorial and incompletely understood. The development of therapies for these disorders of the central nervous system (CNS) is thus far very challenging. Neuroinflammation is one of the processes that contribute to the pathogenesis of CNS diseases, and therefore represents an important therapeutic target. Myeloid cells derived from the bone marrow are ideal candidates for cell therapy in the CNS as they are capable of targeting the brain and providing neuroprotective and anti-inflammatory effects. In this review, experimental and clinical evidence for the therapeutic potential of myeloid cells in neurological disorders will be discussed. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

1. Introduction

A primary goal of regenerative medicine in neurological disorders is to replace the damaged neurons and glial cells, thereby allowing the re-establishment of a functional brain circuitry, resulting in symptomatic relief. Stem cells are the most promising candidates to fulfill such therapeutic goals due to their ability to self-renew and provide neurotrophic factors that promote survival, migration and differentiation of endogenous precursor cells [1–3]. Embryonic stem cells (ESCs), neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) have attracted a great deal of attention for cell therapy in the CNS. However, improvements in the efficiency of the grafted stem cells or stem cell-derived neuronal cells to develop into functional cells and integrate into the brain circuitry *in vivo* are still required. Furthermore, since chronic neuroinflammation is a typical feature of progressive neurodegeneration, grafted neurons may be functionally compromised under these conditions. Another technical hurdle that remains to be solved is how to best deliver the therapeutic cells to their site of action. Due to the limited migratory capacity of stem cells, these need to be administered directly to the damage sites, which may cause additional technical/surgical difficulties.

Bone marrow-derived cells (BMDCs) have long been recognized as a source of autologous adult stem/progenitor cells that are able to colonize the CNS under certain conditions and to contribute to the pool of brain macrophages [4–22]. In a mouse model of Alzheimer's disease, BMDCs were able to phagocytose β-amyloid when resident microglia appeared to be rather ineffective in this task [10–11]. BMDCs were also found to alleviate pathology in other mouse models of neurological and psychiatric disorders, including Rett syndrome [12], Krabbe disease [13], amyotrophic lateral sclerosis [14–17], multiple sclerosis [18,19] and Parkinson's disease [20–22]. The capacity of BMDCs to engraft in the adult CNS makes them attractive vehicles for the delivery of therapeutic genes to sites of brain damage. However, clinical trials with BMDCs in patients with neurological disorders have so far failed to demonstrate robust protective effects [23–25]. The difficulties in translating the preclinical findings to the bedside may result from the incomplete characterization of the bone marrow (BM)-derived cell population that targets the CNS and provides therapeutic effects in neurological disorders. In the past, diverse BM-derived cell populations were applied in clinical trials, which may account for the variability in outcomes [23]. Moreover, host conditioning such as total body irradiation or chemotherapy is necessary for CNS recruitment of BMDCs [7] but has undesired side-effects which warrant the development of new and less invasive conditioning protocols.

2. Myeloid cells for CNS repair

The capacity of bone marrow-derived cells (BMDCs) to migrate to the CNS has long been recognized. These cells target lesion sites in the brain and integrate in the parenchyma as brain macrophages [26–33]. Thus, they are a promising tool for cell-based therapy and gene delivery

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in the CNS [34]. However, it remains to be determined which cell populations within the BM have this property, and whether it is necessary to enrich or purifiy these populations before transplantation in order to achieve the best therapeutic efficiency. Since only a small number (<1%) of transplanted BMDCs reaches the brain [4], it is likely that only a specific cell type is recruited into the CNS from the circulation. However, the precise characterization of this potentially therapeutic cell among BMDCs remains controversial. In chimeric mice generated by total body irradiation (TBI) and BM transplantation, circulating Ly6C-^{hi}CCR2^{+} inflammatory monocytes were suggested to engraft in the brain as macrophages [7]. However, research in parabiotic mice has revealed that BM-derived precursors of brain macrophages are not spontaneously recruited into the bloodstream but need to be artificially administered into the circulation [29]. The authors suggested that committed hematopoietic progenitors are sources of long-lived brain macrophages [30]. However, given the week-long delay in CNS engraftment of BMDCs after TBI and BM transplantation as well as the persistence of BMDCs for more than a year after transplantation [7,30,35,36], short-lived cells such as Ly6C^{hi}CCR2^{+} monocytes [37] or their committed progenitors [30] are not likely to be the source of long-term engrafting BMDCs. Moreover, the short-lived and non- (or extremely low) proliferative BM cell populations are not well suited for *ex vivo* gene transduction or *in vivo* gene delivery approaches to treat chronic progressive neurological disorders. The identification of other hematopoietic stem/progenitor cells, which possess migratory capacity to the CNS and provide long-term supply of protective factors, will be of great value for cell and gene therapy in the CNS.

3. CNS conditioning

The therapeutic effects of BMDCs in clinical trials for neurological disorders will also depend on the conditioning regimens employed during the transplantation procedure. Since the blood–brain barrier (BBB) impedes the systemic delivery of therapeutic cells to the CNS, and BMDCs only target the brain after appropriate conditioning [7], one major technical hurdle that can limit the clinical application of BMDCs is the mode of delivery to sites of brain damage. A particular challenge comes from the fact that many neurological disorders affect large brain areas or even the entire brain, which requires widespread cell delivery. Irradiation-induced changes in the CNS, as well as the introduction of hematopoietic stem/progenitor cells into the circulation, have been suggested as mandatory conditions for the recruitment of BMDCs into the brain [7,29,30]. Although TBI is an effective conditioning protocol to target BM-derived myeloid cells to the brain, this myeloablative treatment induces CNS inflammation and disturbance of the host's hematopoietic system [7,38]. In the past, TBI has played an important role in patients undergoing HSC transplantation. However, TBI may result in serious acute graft-*versus*-host disease (GVHD) causing transplant-related morbidity and mortality, as well as damage to non-target tissues, which may predispose to GVHD or enhance the clinical manifestations of acute GVHD [39–41]. Recently, the alkylating chemotherapeutic agent, busulfan, has been suggested as an alternative conditioning procedure for BMDC engraftment in the brain [38]. In fact, high intensity myeloablation with busulfan has been used successfully in hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy [42]. However, BMDC engraftment at sites of CNS damage is dramatically reduced compared to irradiation [38] or even absent [43] after busulfan conditioning in mice. Recently, low-intensity, non-myeloablative conditioning protocols (*e.g.* cyclophosphamide, melphalan, fludarabine-based, or the BEAM combination of cyclophosphamide, cytosine arabinoside, etoposide and melphalan) have been used as alternatives for BMDC transplantation in neurological disorders [23]. In addition, focal irradiation may serve as a conditioning regimen that results in less tissue damage and the possibility of dose escalation compared with conventional TBI [39]. Together, an efficacious host conditioning strategy will guide the success of BMDC transplantation in CNS disorders.

4. Therapeutic potential of BMDCs

The experimental evidence of hastening recovery in neurological disorders by the transplantation of BMDCs has been mounting over the last decade. In rodent models of neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis, direct intracerebral grafting or systemic administration of BMDCs improved functional recovery [10,11,14–19]. The therapeutic potential of BMDCs has also been confirmed in first clinical trials in human patients.

4.1. Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disorder of the brain and spinal cord with unknown etiology and unpredictable course. Evidence indicates that MS is a multifactorial trait caused by both genetic and environmental factors. MS affects all ages, mostly between the ages of 18 to 50 years. Four disease courses have been categorized: 1) Relapsing-Remitting MS (RRMS); 2) Secondary-Progressive MS (SPMS); 3) Primary-Progressive MS (PPMS) and 4) Progressive-Relapsing MS (PRMS) [44]. RRMS is the most common disease course (85%) that mostly affects young individuals (~20 years). The symptoms manifest as relapsing neurological deficits that are associated with inflammatory attacks of immune cells on myelin as well as the nerve fibers themselves. Patients develop episodes of neurological dysfunction that last for several weeks, and are followed by substantial or complete recovery. In this disease course, the location of the damage and the resulting symptoms vary between individuals. Unlike RRMS, the progressive types of MS (SPMS and PPMS) involve much less neuroinflammation and, typically, are first diagnosed after age of 40 years. PRMS is the least common disease course, in which patients experience continuous neurological dysfunction, in addition to occasional relapses like those experienced by RRMS without complete recovery. Currently, PRMS is newly categorized as PPMS [45].

While the etiology is still unknown, MS is widely considered as an immune-mediated disease, initiated by environmental factors triggering activation of encephalitogenic T cells [46]. Infiltration of autoreactive T cells through the BBB initiates a transient inflammatory response, which then leads to a breakdown of the BBB and, subsequently, an influx of immune cells/molecules, such as monocytes, macrophages, nature killer (NK) cells, B cells, and complement factors. This neuroinflammation results in myelin destruction, induced oligodendrocyte mortality and, finally, neurological deficits. In a murine model of MS called experimental autoimmune encephalomyelitis (EAE), inhibition of monocyte infiltration into the CNS completely blocked EAE progression, underscoring the important role of monocytes in the development of disease severity [30,47].

Based on the suggested pathogenesis, on-going therapies for MS embrace immunomodulatory and immunosuppressive approaches that, unfortunately, have shown limited efficacy in patients with either a progressive or an aggressive course [48]. Hematopoietic stem cell transplantation (HSCT) has long been suggested to control or even cure refractory cases of MS due to the ability to temporarily eradicate the autoreactive immune cells and to reinitialize the aberrant immunity to self-antigens [49–65] (Table 1). In EAE, while BM transplantation performed at the peak of the disease resulted in accelerated recovery [51], no protective effects was seen when the treatment was carried out in the chronic neuroinflammatory phase [52]. Similarly, in MS patients treated with HSCT the therapeutic effects on progression of neurological disability were generally of short duration, and only partially confirmed in longer follow-ups (Table 1). The highest therapeutic efficiency was seen in MS patients with active neuroinflammation [53–56], a short disease duration [55,57] and a lower clinical score