Stem cell and progenitor cell transplantation in multiple sclerosis: The discrepancy between neurobiological attraction and clinical feasibility

Hans Lassmann*

Center for Brain Research, Medical University Vienna, Spitalgasse 4, A-1090 Wien, Austria

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Abstract

Recent developments in our understanding of stem— and progenitor cell differentiation raises hopes that brain damage in chronic neurological diseases may become repaired by systemic or focal transplantation of such cells. In this review the potential of such an approach is discussed, but it is also highlighted that many aspects regarding its feasibility or safety are currently unresolved. Furthermore, recent findings on the pathogenesis of multiple sclerosis lesions indicate that major problems in this disease rather are related to axonal pathology and neurodegeneration rather than to the absence of oligodendrocyte progenitor cells within the lesions. In light of this complex situation, it is concluded that clinical trials of stem— or progenitor cell transplantation in multiple sclerosis are currently premature.

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1. Introduction

Major advancements have been achieved during the last years in our understanding of the biology of stem cells and their potential to differentiate into neurons and glia. This opens new perspectives for therapy of human brain diseases and it is hoped that defects in the central nervous system may either be prevented or repaired through the transplantation of undifferentiated stem cells or predetermined progenitor cells [1–4]. Multiple sclerosis is thought to be one of the most attractive candidate diseases for stem—or progenitor cell transplantation, since the primary defect appears to be immune mediated primary demyelination and the loss of myelin could be compensated by providing new myelinating cells within the lesions. However, considering the so far established stem cell technology, the nature of the biological defect in multiple sclerosis and possible safety issues, it seems that immediate use of such therapies in MS patients at the present time is premature and it is far from clear, whether stem—or progenitor cell transplantation will have a major impact on MS therapy in the future.

2. What are the aims of progenitor—or stem cell transplantation in multiple sclerosis?

Stem cells or progenitor cells can reach the central nervous system either following direct intracerebral transplantation or through the blood stream.

2.1. Intracerebral transplantation

The first and most straightforward approach is to provide progenitor cells for the formation of new myelin in established demyelinated plaques [2,5,6]. Indeed, ample experimental evidence provides compelling evidence that demyelinated lesions can become remyelinated by transplantation of cells, which have the capacity to differentiate into mature oligodendrocytes or Schwann cells. There are however many practical obstacles for such an approach in a disease like multiple sclerosis [6,7]. First we do not know, what cells are the best suitable for this purpose in vivo. Schwann cells are most easily obtainable, even as syngeneic cells, but their spread into and their remyelination potential in the CNS tissue is massively impeded by the presence of astrocytes. Whether olfactory ensheathing cells, a cell population which shares some properties of central and
peripheral myelinating cells, are more suitable in in vivo conditions of demyelinated plaques has to be established. The use of oligodendrocyte progenitors or even neural stem cells could provide a true source of new oligodendrocytes, but it is difficult to believe, why such cells should not become targets of the immune attack within the MS lesions.

The second major obstacle is that multiple sclerosis is a multifocal disease, which affects a brain, in which a single MS plaque is larger than the whole brain of small rodents, the animal species generally used to test for the efficacy of stem—or progenitor cell transplantation. It is unlikely that progenitor cells will spread through the whole human brain and spinal cord in an extent, which will allow them to remyelinate and repair multiple large demyelinated plaques at completely different locations. Thus this approach of focal transplantation of remyelinating progenitor cells will be restricted to a single or only very few lesions in the individual patient. It may, however, become attractive in treating single clinically important “strategic” lesions for instance in the brain stem.

2.2. Systemic transplantation

Recent studies showed that neuronal stem cells express on the surface a set of adhesion molecules and chemokine receptors, which bears resemblance to that in hematopoetic progenitor cells or leucocytes. Thus, when such cells are injected into the circulation they can leave the blood stream and migrate into different tissues, including the central nervous system [8]). Even more importantly, these cells preferentially home into areas of the central nervous system, which are damaged. As an example in mice with autoimmune encephalomyelitis intravenously injected neural stem cells migrate into the inflammatory demyelinating CNS lesions and this is associated with a decrease in the severity of clinical disease and a reduction of pathological alterations in these lesions [8]. How these cells mediate this beneficial effects is less clear. Apparently they stay in the CNS lesions in a rather undifferentiated stage. They in part become oligodendrocytes and seem to be directly involved in remyelination. In addition they may mediate their beneficial effect by secreting neurotrophins, which may reduce directly the injury of CNS cells or may stimulate endogenous remyelination [8]. In addition, neurotrophins may have a direct immunosuppressive effect, for instance by reducing the expression of proinflammatory cytokines [8] or MHC molecules or by inhibiting monocyte recruitment into the lesions [9]. Although it seems to be very attractive to cure degenerative lesions in the CNS just by intravenous injection of stem cells, there are, as will be discussed below, major concerns regarding the safety of this approach.

2.3. Bone marrow transplantation

Obviously, the major objective for bone marrow transplantation is to correct the putative autoimmune reaction, which is thought to drive the destructive process in the nervous system of MS patients [10,11]. The problem of this approach, however, is that it is currently uncertain, whether brain inflammation is alone responsible for the destruction of myelin sheaths, oligodendrocytes and axons in MS patients.

In addition, however, recent studies have suggested that bone marrow stem cells have a broad differentiation potential, giving rise for instance to new neurons [12], possibly even in humans [13]. This may open new avenues for brain repair in chronic neurological diseases, including multiple sclerosis. Although some studies claim that such a transdifferentiation may occur in vivo, the evidence for this is currently controversial [14]. If present at all, there are only very few CNS resident cells, in particular Purkinje cells in the cerebellum, which carry the bone marrow marker in the respective chimeras. Furthermore, it has been shown that bone marrow derived cells may fuse with cardiomyocytes, hepatocytes and Purkinje cells even in vivo, which could erroneously be interpreted as trans-differentiation following bone marrow transplantation [15]. Thus, at the present moment it is not clear, whether bone marrow stem cells can replace neurons and glia at all in vivo and if it is the case, whether it occurs in an amount, which is sufficient for the repair of CNS lesions.

3. Is multiple sclerosis really a good candidate disease for transplantation of neural stem cells or progenitor cells?

The original aim of stem cell or progenitor cell transplantation in multiple sclerosis was to repair the demyelinated plaques in the central nervous system. Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system, which implies that myelin and oligodendrocytes are preferentially lost from the lesions [16]. Although axons are affected too in the disease process, they are at least partially preserved within the demyelinated plaques. In addition to the pronounced axonal degeneration, which occurs in actively demyelinating lesions, there is a slow burning chronic axonal injury in established inactive plaques, which is absent in remyelinated lesions [17]. For this reason the induction of myelin repair in MS lesions may not only improve function, but may even protect axons from further chronic damage.

Recent studies, however, suggest that there is no simple strategy to improve remyelination within MS plaques. Spontaneous remyelination is a regular feature at early stages of lesion formation in MS and remyelination may be quite extensive in some cases, but absent in others [18,19]. Thus in certain MS cases most lesions within the CNS have the appearance of shadow plaques, which are known as areas of complete remyelination [20]. Since so far no imaging techniques are available to distinguish demyelinated from remyelinated shadow plaques in MS brains, the proper selection of MS lesions for cell transplantation is difficult if not even impossible at the present time.
In addition, it has been shown recently that many MS plaques may contain high numbers of oligodendrocytes or their progenitor cells even in the absence of remyelination [21–24]. Thus, there are cells present, which in principal have the capacity to remyelinate, but they do not accomplish this task [25]. Some data suggest that the failure of remyelination is less a problem of oligodendrocyte progenitor cells, but may be due to a defect of axons, which does not allow remyelination to occur [26]. In such a situation the transplantation of additional oligodendrocyte progenitor cells will not solve the problem. Furthermore, it has to be considered that axonal loss in chronic MS lesions generally is substantial and permanent functional deficit in MS patients appears to be closer related to axonal loss than to demyelination [27,28].

Finally, there is an additional component of multiple sclerosis pathology, which may occur independent from the formation of demyelinated plaques. This is particularly prominent in patients with primary or secondary progressive MS and consists of a diffuse axonal injury in the so called “normal” white matter. The pathogenesis of this type of tissue injury is not clear so far. It has been suggested that diffuse axonal injury in the white matter may reflect axonal transsection in the plaques with subsequent Wallerian degeneration in the respective tracts [29]. However, this explanation does not account for extensive diffuse white matter injury, which may occur in patients with primary progressive MS on the background of only very few and small focal demyelinated plaques. Whether this diffuse brain injury in patients with progressive MS reflects a neurodegenerative component of the disease, which is independent from inflammation or is driven by the inflammatory response is so far undetermined [30,31]. Since this type of pathology mainly affects axons, leading to secondary destruction of myelin, a therapy, which stimulates remyelination, will have little effect on this particular aspect of the disease.

Thus, transplantation of oligodendrocyte progenitor cells into MS lesions may be beneficial only in selected patients and (clinically important) lesions, in which it is clear that they are not spontaneously remyelinated and the failure of remyelination is not due to loss or a functional defect of axons. So far there are no tools available to identify such lesions in the living MS patient.

An alternative strategy appears to be followed by applying neural stem cells through the circulation by intravenous injection. As shown in experimental studies such cells can preferentially home into inflammatory demyelinating lesions and exert locally a neuroprotective function [8]. Interestingly, these cells apparently do not locally differentiate into neurons or glia cells, but remain in an undifferentiated stage. It is assumed that they exert their neuroprotective function through the secretion of cytokines or neurotrophins. Such a mechanism is potentially interesting, since it may not only be neuroprotective, but may also suppress a pathogenic immune response.

4. Safety issues

There are two major safety issues in relation to the transplantation of stem cells or progenitor cells in multiple sclerosis patients: the immunological risks and the possible oncogenic potential of the transplanted cells.

Immunological problems may mainly arise, when stem cells or progenitor cells are directly transplanted into the inflammatory environment of a MS lesion. This may be minimized by the use of syngeneic cells, although this approach is limited for obvious practical reasons. Although transplanted oligodendrocyte progenitor cells survive and migrate a considerable distance in inflammatory demyelinating lesions [32], there is no reason to believe that such cells, when they differentiate into mature oligodendrocytes and form new myelin, will escape the ongoing immune attack within the lesion. Even more problematic is the transplantation of allogeneic cells. Minor mismatches in MHC antigens may locally boost the immune reaction and aggravate the preexisting disease.

Another issue deals with a possible oncogenic potential of the cells. In general, oligodendrocyte progenitor cells are committed to further differentiate into myelinating cells and therefore their oncogenic potential may be minor. It has, however, to be kept in mind that most studies have been performed in short term experiments and it is largely unknown, how these cells behave, when they remain within the brain for years. Even more worrying is the observation, that neural stem cells, which are transferred intravenously, can reach the brain lesions and in part remain there in an undifferentiated stage [8]. Although in this study there was no evidence for tumor formation within the relatively short observation period, a situation like this bears similarities with a condition in humans, known as gliomatosis cerebri [33]. This condition leads within a time period of several years to gradual overgrow of the whole brain with glial cells, which appear to be derived from progenitors. It may become very difficult to rule out such a potential risk in experimental models.

5. Conclusions

The repair of brain lesions by stem cells or specific progenitor cells is a very attractive approach, which currently receives major attention in biomedical research. Indeed, in case it works, it may solve the most important problem of CNS disease, the lack of regeneration and repair. So far, however, there are many open questions and problems regarding the feasibility of this approach and safety issues. In addition, recent data on its pathogenesis raise some doubts that multiple sclerosis will be a prime candidate disease for such transplantation strategies. From all these data it seems clear that clinical studies on stem cell or progenitor cell transplantation in multiple sclerosis patients are currently premature.
References


