Review paper

Neural stem cell therapy in neurological diseases

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Abstract

Early developmental process of mammalian embryo is almost completely directed by the behavior of stem cells, which is controlled by both environmental and intrinsic factors. These cells commonly subject to dividing, migration, deterioration or death. Comparing to all other tissues in the body, central nervous system has a considerably limited capacity to regenerate. Recent knowledge on neural stem cells has brought novel approaches as to the use of stem cells in the treatment of some neurodegenerative disorders such as Parkinson, Alzheimer disease and amyotrophic lateral sclerosis, as well as in the management of spinal cord injuries. However, scientific literature requires detailed information regarding the proliferation and differentiation of stem cells and the mechanisms controlling the migration of these cells to the targeted central nervous system site. Development of new therapeutic protocols using stem cells and their effective clinical application in the future would bring light to cope with a number of systemic diseases, especially neurological disorders. This review has considered the biological features of stem cells, stem cell plasticity, potential application of stem cells in neurological diseases and cancer, highlighting the promises as well as the problems of this treatment approach.

Key words: neural stem cell, neurodegenerative disease, migration.

Introduction

Stem cells are unspecialized cells that develop into the specialized cells that make up the different types of tissue in the human body. They are vital to the development, growth, maintenance, and repair of various organs such as brain, bones, muscles, nerves, blood and skin. Stem cells are controlled by both environmental and internal factors. These cells always face to division, migration, attrition, and death [1]. Embryonic stem cells, which can be derived from a very early stage in human development, have the potential to produce all of the body's cell types. The early period of developmental process of mammalian embryo totally depends on the behavior of embryonic stem cells. Those cells know what to do and where to migrate in order to form the structure of the living organism. Adult stem cells, however, are found in certain tissues in fully developed humans, from babies to adults; and may be limited to producing only certain types of specialized cells [1].

Unlike many other tissues in the human body, central nervous system (CNS) has a limited capacity to regenerate. However, neural stem cells can regenerate themselves and bear the ability to form immature precursor and adult cells which is a trait encountered in neurons and glial cells. Recently,

the information obtained about neural stem cells has sparked a hope for employment of stem cell as regeneration and cell replacement therapy in the treatment of various neurodegenerative diseases (such as Parkinson's and Alzheimer diseases), cerebrovascular diseases (i.e. stroke) and injury (e.g. spinal cord) [2, 3].

Majority of neurons in a developing nervous system, migrate to their destined target sites. Disruption of migratory mechanisms might lead to lethal outcomes causing malformations or tumors. Over the past 80 years, brain tumours were thought to originate from the cell types of the adult brain that they resembled most, as assessed by comparison of histological features, e.g. astrocytomas were thought to arise from astrocytes, oligodendrogliomas from oligodendrocytes, ependymoma from ependymal cells. However, this concept is being increasingly challenged and the role of neural stem cells or progenitor cells in brain tumour formation is currently being investigated [4]. Studies on neural migration provide us helpful data to better understand the important mechanisms of normal development of nervous system and give us information on the etiology of diseases originating from migratory deviations, and therefore, enable us to create new treatment strategies against neurological diseases [1].

Routine protocols and methods have been available in the treatment of neurodegenerative diseases that are characterized by progressive degeneration of selective neuronal population; however, the efficacy of the known treatment modalities is incompetent and the characteristics of the pathology in neurodegenerative diseases make them good candidates for cell therapy. Human bone marrow-derived mesenchymal stem cells can be easily amplified *in vitro* and their transplantation in neurodegenerative diseases, as well as in spinal cord injuries, has proven to be feasible, safe, and potentially effective [5, 6]. As a fact that available cell therapy protocols mostly involve in the use of hematopoetic, but not the neural, stem cells, introduction of neural stem cell therapy to these treatment modalities is a novel and striking subject in this area. Like bone marrow-derived stem cells, neural stem cells also have the capacity for self-renewing, and it is possible to culture and expand these cells and their progenitor cells for use in cell therapy regimens [7]. Comparing to transdifferentiation capacity of the hematopoetic stem cells, an important handicap of neural stem cell use is the inadequate differentiation of the progenitor cells to neural stem cells which requires promotion with some trophic factors, i.e. brain-derived neurotrophic factor [8]. Current studies are mostly experimental on animal models, however promising [9-11].

Before stem cells can be applied to human medical problems, substantial advances in basic stem cell biology and clinical technique are required. Therefore, this paper aimed to review current available literature reports on neuronal stem cell biology and to summarize information on stem cell processes such as proliferation, differentiation, and migration to spesific target sites in CNS.

Stem cells

Several rules have been determined to identify a cell as stem cell. The cell should have the ability of division and regeneration for a long term alongside being unspecialized. A daughter cell obtained from stem cells should have the quality of replenishing specialized cells. Following stem cell transplantation to the damaged recipient, parent tissues can be functionally regenerated [12-14].

First stem cell in developed mammalians is known to be the egg. This cell is totipotent and forms both embryo and placenta. Embryonic stem cells generate the inner cell mass of blastocyte. Since these cells have the potential to form many different cell types in the new embryo, they are described as *pluripotent*. Other stem cells involved in the later periods of development, localize in different organs where they can develop into the mature cells building the specialized tissues [15-18]. The main purpose behind division of stem cells, is to maintain a constant amount of stem cell population and produce limited number of specialized cells. Therefore, the division of those cells exhibit an asymmetric characteristic. While one of the dividing stem cells differentiates into mature progenitor cells, the other may remain as a stem cell [16, 17].

Several new methods and protocols have been established to identify, isolate, and characterize live neural stem cells in terms of their capability to proliferate and differentiate [19]. Neural stem cells can be isolated by flow cytometric methods based on physical properties such as size (forward scattering), granularity (side scattering), and expression of surface antigens [20, 21]. Therefore, removal of these glial cells using physical parameters is beneficial prior to cell transplantation.

Despite the identification describing stem cells as having the ability of "unlimited division", this does not happen in a very short duration of time, but expands over a long period of time. Actually, many stem cells display a low rate of division [17]. In mature mammalian tissues, along with nervous system, the following structures harbor a certain amount of stem cell population, as well: bone marrow, muscle tissues, intestines, pancreas, liver, epidermis [22-24]. Those cells, which are also named as somatic stem cells, involve in maintaining homeostasis and restoration of the damaged tissue [25]. During embryonic differentiation process, neural stem cells are localized in two important germinal layers of anterior brain: ventricular zone

and subventricular zone. Those areas are the places where all the neurons and glial cells increase in numbers [26, 27]. These neural stem cells housed in germinal layers, have been a focus of studies since the advent of the differentiation of cell groups in brain. Those cells generate the spherical cell clusters called as "neurosphere". Neurospheres have the ability of generating new neurons, astrocytes, and oligodendrocytes [26].

Stem cell plasticity

Until recently, the differentiation profiles of stem cells were believed to take place within an organ and thought to be confined to considerably specific environments in an isolated way. However, it is well known that somatic stem cells exhibit a higher degree of differentiation capacity [1, 3, 28]. It has been reported that transplantation of stem cells in an adult brain exposed to radiation to the bone marrow of rats results in the differentiation of these cells to the bone marrow cells which generate blood cells [29]. Moreover, the transdifferentiation has been reported to be between different types of somatic stem cells [30, 31]. Bone marrow cells have been shown to differentiate to hepatocytes [18, 32, 33], myocardial cells [34], muscle cells [35, 36], or nerve cells [37, 38].

The hepatocytes have been shown to turn into pancreatic islets which was a remarkable event [39]. Muscle cells have the potential to differentiate into hematopoietic cells [40] or generate adipocytes [41]. Furthermore, whereas skin cells can differentiate into nerve cells [42], CNS stem cells can differentiate into muscle cells [43, 44]. The injection of adult nerve cells into embryo during blastula phase generates the cells belonging to three germ layers [45]. Neural stem cells have been shown to rarely transform into blood tissue [29]. At least one of the results given as "stem cell plasticity", are proposed to be a possible cell fusion [46]. In those studies, co-culturing of somatic stem cells with embriyonal stem cells is asserted to lead to a fusion between these two cell types [46]. Cord blood stem cells and neural stem cells have been cultured together by using neural growth factors [47]. Recently, many studies have been published showing the presence of new and migrating stem cells in many rodent brain damage models and the presence of new neurons in adult human hippocampi; however, there are also reports indicating contrary results [48]. Those results have elevated the interest for using regenerative medicine against neurologic diseases which are ranked as the hardest ones to cure. Initially, cell therapy has been thought to have a "cell replacement" mechanism, however, many evidences have indicated a trophic or supportive influence in damaged tissue or brain. Angiogenesis and neurogenesis in brain exhibit a parallel course [48].

Use of stem cells in neurological diseases

One of the main targets of neurologists and neurosurgeons is to find a way to prevent negative influences of brain diseases, particularly neurodegenerative ones. Only a few molecules which are capable of curing and even stopping the progression of symptoms, could have been developed; therefore, cell therapy continues to be a current topic of high interest. Today, investigations are focused on two main treatment strategies:

- "replacement", grafting cells which have the capacity to differentiate into appropriate cells and restore the lost functions; and
- "neuroprotective" or "protective", increasing the resistance of remaining cells against the surrounding toxicity and enhancing the self-renewal mechanisms of the body [49].

As mentioned before, CNS holds a very weak regenerative capacity. Despite presence of stem cells in adult brain, those cells exhibit a very limited ability for regenerating new neurons following an injury. As the pool of data on neural stem cells accumulate, new hopes and horizons are cleared for the treatment of various diseases such as Parkinson disease, Huntington chorea and multiple sclerosis; as well as the ischemic brain damage [50]. There are also experimental animal studies which show that neural structural change is possible [51]. In organ transplantation studies conducted with experimental models of Parkinson disease, grafted dopaminergic neurons have been shown to release dopamine at normal levels and a significant behavioral recovery has been detected in the animals [52, 53]. Similar results were obtained from humans receiving clinical treatment, as well [54-56].

Moreover, promising results have been reached for Huntington disease as well. Clinical positive developments of motor and cognitive functions, were shown on several animal studies [57, 58] and clinical trials [59, 60]. Use of mesenchymal stem cells in debilitating diseases such as amyotrophic lateral sclerosis [ALS] is another matter of debate. Amyotrophic lateral sclerosis is a pathology that causes a selective loss of motor neurons leading to a progressive decline in muscle functionality and poor prognosis. Direct injection of mesenchymal stem cell suspension into the spinal cord of ALS patients has resulted in a mild trend toward a slowing down of muscular strength decline three months after cell implantation [61]. A recent study has reported that one-year follow-up of 13 ALS patients treated with bone marrow-derived hematopoietic progenitor stem cells results in a significant improvement in 9 patients as confirmed by electroneuromyography [62].

Stroke is the third leading cause of death in Western countries and more importantly a leading cause of adult disability. Stem cell therapies are an

important strategy for the treatment of stroke, as well [63]. The tissue damage could stimulate the stem cells migration, and they track into the site of damage and then undergo differentiation and promote structural and functional repair via stem cell plasticity. The plasticity functions of stem cells in injured tissue are dependent on the specific signals present in the local environment of the damaged tissue. Restorative approaches by cell-based therapies are clinically appealing as it might be possible to help patients even when treatment is initiated days or weeks after the ischemic insult. An extensive number of experimental transplantation studies have been conducted with cells of different origins (e.g., embryonic stem, fetal neural stem, human umbilical cord blood) with promising results [64-66]. Noninvasive intravascular administration of cells, which provides a broad distribution of cells to the close proximity of ischemic tissue, has perhaps the most immediate access to clinical applications. However, concerns have been raised over the safety of this experimental therapeutic approach, including, for example, whether there is the potential for malignant transformation of transplanted cells. Indeed, a recent case report has revealed a donor-derived human brain tumor complicating neural stem cell therapy; suggesting that neuronal stem/progenitor cells may be involved in gliomagenesis [67].

Transplantation of stem/progenitor cells for spinal cord injury is another area of interest in stem cell research. It has recently been reported that contusive spinal cord injury in the rat results in devastating pathology and that there is a significant loss of mature oligodendrocytes and astrocytes, which is subsequently followed by an increased proliferation of endogenous NG2[+] cells [68]. This process is important for functional recovery and this endogenous progenitor cell response might be mimiced by cell transplantation. Indeed, it has been observed that neurospheres cultured from the periventricular region of the adult spinal cord contain neuronal stem/progenitor cells and transplantation of these neurospheres into the intact spinal cord results in proliferation; by one week posttransplantation, these grafted cells primarily expresses an oligodendrocytic phenotype and only 2% differentiates into astrocytes [69]. Furthermore, transplantion of the neurospheres into the injured spinal cord has resulted in the differentiation of the transplanted cells primarily into astrocytes and oligodendrocytes and a functional recovery was observed as well [70]. Apart from direct injection into the injury site, grafting of stem cells intratechally via lumbar function also has resulted in localized accumulation of cells at the injury site, neuroprotection, and modest recovery of function [71]. Positive results of animal studies has led to clinical studies. It has been reported that intravenous application of bone marrow stromal cells to animals and patients with spinal cord injury reveal varying degrees of improvement that appear to fall within an expected range of spontaneous recovery [72, 73]. However, a recent case report of a two-year haematopoietic stem cell therapy of a complete spinal cord injury patient has revealed that stem cell therapy did not have any beneficial effect on the repair of the spinal cord in this patient [74]. Further research is needed to improve and justify the clinical application of stem cell therapy in spinal cord injury.

Neural progenitor cells administered into the circulation of multiple sclerotic animals were shown to be capable of passing through blood-brain barrier and migrating towards the areas of inflammation [75]. Fresh fetal tissue is the cellular source for human clinical studies, however, due to the failure to standardize cells and limited number of cell content, no satisfying results could have been obtained yet. Employment of abortus material of fetuses has been an ongoing intense ethical concern [49, 51].

Neural stem cells can transform into many types of cells *in vitro* and constitute a large cell population. Cultured neural cells, may be a solution for the technical and ethical problems arising from use of fresh tissue as treatment source in transplantations [49, 50].

Another possibility may be to create strategies which activate the endogenous stem cell pool in brain [76]. However, before clinical trial, we need more in-depth information on biology of neural stem cells.

Stem cells in relation to cancer

Stem cells and cancer cells are very similar in certain traits. Cancer cell originates from a single cell. Similar to stem cells, cancer cells bear an unlimited ability for proliferating themselves. Moreover, tumors are of heterogenous character and include differentiated cells of different levels. Expression of neural stem cell marker Nestin, has been shown in primitive neuroectodermal tumors and other tumors with high malignancy [77, 78].

Recently, a protein called "nucleostemin" has been reported to be present in neural stem cells and tumor cells, despite its absence in several differentiated cells [79]. Increasing knowledge on neural stem cells may shed a light on development of CNS tumors. Moreover, stem cells are proposed to be a valuable method in treatment of CNS tumors. The migratory ability of the stem cells in CNS enable them to be used for producing therapeutic proteins and to be employed as a cellular vector for gene transfer as well. When neural stem cells are implanted into the gliomas of adult rodents, they were observed to surround the

spreading tumor; furthermore, their implantation in remote sites to the tumor, has revealed their ability to migrate long distances towards a tumor [80, 81]. Recent molecular imaging techniques with cell-labelling strategies can be used to monitor the seeding and migration of embryonic stem cells [82, 83]. Neural cells were shown to transport tumor necrosis factor to the invasive glioma cells *in vivo*, which indicates their inductive role on apoptosis of tumor cells [84].

Cancer stem cell hypothesis is based on the fact that all cells do not have the same proliferation potential and that most proliferative cells with major contribution to the tumor development in brain tumors have similar phenotypical and functional characteristics with the normal neural stem cells. Recently, different investigators have shown that cancer stem cell isolated from human brain tumor tissue (glioma and medulloblastoma) exhibited self-regeneration and multi line cell differentiation [85, 86]. Moreover, implantation of cancer stem cells obtained from those tumors into the rodent brain, leads to generation of tumors similar to the parental tumor; this observation indicates that progenitor/stem cells can regenerate their neoplastic phenotypes *in vivo* [85, 86]. All those studies evoked questions on role of stem cells over brain tumors and their development and treatment.

Malignant primary brain tumors are characterized with shortness of mean survival period and 100% tumor-related mortality. Despite novel chemotherapeutic treatments, very little improvement in overall survival rates could have been achieved and radiotherapy only provides a temporary benefit; this profile attests the fact that most of the cases are resistant against treatment. Lately, several studies showed that a small group of cancer stem cells as having the ability to reincrease the number of tumor cells along with orientating malignant development and mediating resistance against radiotherapy and chemotherapy [87]. Future treatment approaches will most probably shift from elimination of the group differentiating from tumor cells while undergoing division, to targeting and elimination of a small number of self-regenerating tumor cells. While cancer stem cell hypothesis receives a certain amount of recognition; the theoretical, technical aspects and interpretation of the data supporting the hypothesis, require further explanations. Cancer stem cell hypothesis brings about a hope that it would cause significant changes in terms of tumor classification and treatment [for a recent review see 87].

In conclusion, predicting future developments in the area of neural stem cells, appears to be difficult. Neural stem cell topic has caused quite a stir with many novelties and discussions in a short period. However, it is an undisputed reality that accumulation of datas on neural stem cells, will shed a light on yet unrevealed development of CNS at molecular level. Recently, the studies have been focused on two important topics: neurodegenerative diseases and cancer. Stem cell technologies play an important part in clinical treatment of neurodegenerative diseases, however, orientating stem cell differentiation towards a target neural cell phenotype, remains to be a contentious field alongside several problems regarding clinical application of neural stem cells. Since this is a new and very rapidly evolving area, the recommendations towards patients should be elaborated carefully. Main problems appear to be the selection, generation, implantation, and finally disposal of stem cells. In future, generation of stem cell treatment protocols and implementation of a more efficient integration to clinical practice, will certainly bring about new hopes for providing a solution against many systemic diseases, particularly neurological ones.

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