Review Article

Prospects for regeneration therapy with stem cells

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"Stem cells" is the general term for cells that have the ability to renew themselves and the ability to differentiate into the cells that compose tissues. Stem cells possess a combination of "pluripotentiality", which is the source of their ability to differentiate into various cell types that compose tissues and to fulfill their functions, and "self-renewal" ability, which replenishes "stem cells" themselves in the undifferentiated state by cell division.

Stem cells or undifferentiated cells in vertebrates[1-4], are broadly classified into two types: stem cells in the embryo stage, and adult stem cells, which are present in the tissues of adults. When organs are formed during embryonic stage, organogenesis is achieved by vigorous renewal by embryonic stem (ES) cells, which have very high proliferative capacity, and by orderly differentiation of tissue cell groups (patterning)[1-4]. ES cells are cells in the initial state when the fertilized egg is in the process of dividing, and since they harbor the ability to become any stem cells required for embryonic tissue-patterning, they are also called pluripotent stem cells. Induced pluripotent stem cells (iPS cells)[5, 6] are artificially produced stem cells that are endowed with the same pluripotency to differentiate as these ES cells. In theory, cells that possess this pluripotency are able to differentiate into the constituent cells of every organ and tissue in the body. Therefore transplantation-based therapeutic application by using autologous cells as the source of production of iPS cells came closer to becoming a reality. Furthermore, established iPS cells from various diseases can also provide human stem cell resources for pharmacological, diagnostic or genetic evaluation.

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Recent studies have demonstrated the widespread distribution of a population of cells in the human body which has the potential to renew themselves. Adult stem cells are stem cells that are present in the body of fully grown human beings (adults), and are not stem cells derived from ES cells or embryonic organogenesis stage. They are also called "somatic stem cells". Adult stem cells are endowed with multipotentiality that is "restricted" to the constituent cells

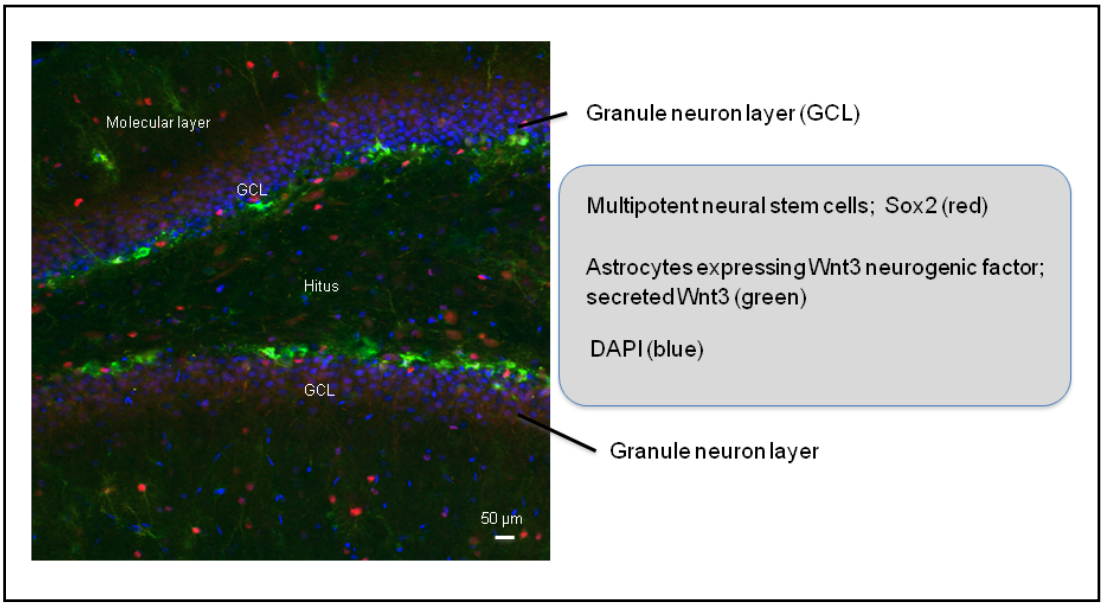

Fig.1 Neural stem cells and the niches at dentate gyrus of adult hippocampus
Cells at inner layer of at dentate gyrus region consist undifferentiated neural stem cells population and the niches that supports adult neurogenesis.

of the tissue in which they are present, and with a capacity for self-renewal. For example, the hematopoietic stem cells in bone marrow are restricted to being able to differentiate into the constituent cells of the blood cell system: leukocytes (neutrophils, eosinophils, basophils, lymphocytes, monocytes, and macrophages), erythrocytes, platelets, mast cells, and dendritic cells. There are also various other types of adult stem cells, including the fat stem cells contained in adipose tissue, liver stem cells that produce the liver, skin stem cells that become skin tissue, intestinal stem cells that produce intestinal tissue, and germ stem cells that give rise to germ cells[7-17]. Adult stem cells consist proliferating cell populations that react depending on environmental various changes in our life throughout adulthood. Their self-renewals and differentiations into the required constituent cells occur in the various tissues on a regular basis[7-17]. Even if tissue is lost from the skin, liver, heart, kidneys, lungs, blood, etc., newborn cells are produced to some extent, the lost functions are reproduced by the stem cells in the tissue itself, and they are able to compensate for those functions[7-17]. The greatest progress in adult stem cell research has been made in research on neural stem cells.

What are adult neural stem cells?: Historical background

There is a historical background to the reason why research on adult neural stem cells has flourished, and the background is that for about 100 years it was thought that the central nervous system (brain and spinal cord) was not endowed with the ability to regenerate.

"Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated." - Santiago Ramon y Cajal[18].

When the adult brain is injured, sometimes the remaining nerve cells form new connections with other nerve cells, and they compensate for some of the lost functions. The repair mechanism is thought to be postmitotic, such as sprouting of axon terminals, changes in neurotransmitter-receptor expression. The widely accepted notion that nerve cells themselves do not regenerate, and that the brain is an inviolable tissue that possesses a fixed amount of memory and information processing ability was believed for a long time.

However, since the early 1990s, a large body of work has demonstrated that new neurons are indeed generated in restricted regions of the adult mammalian central nervous system (CNS)[19-26]. Many researchers reported the phenomenon

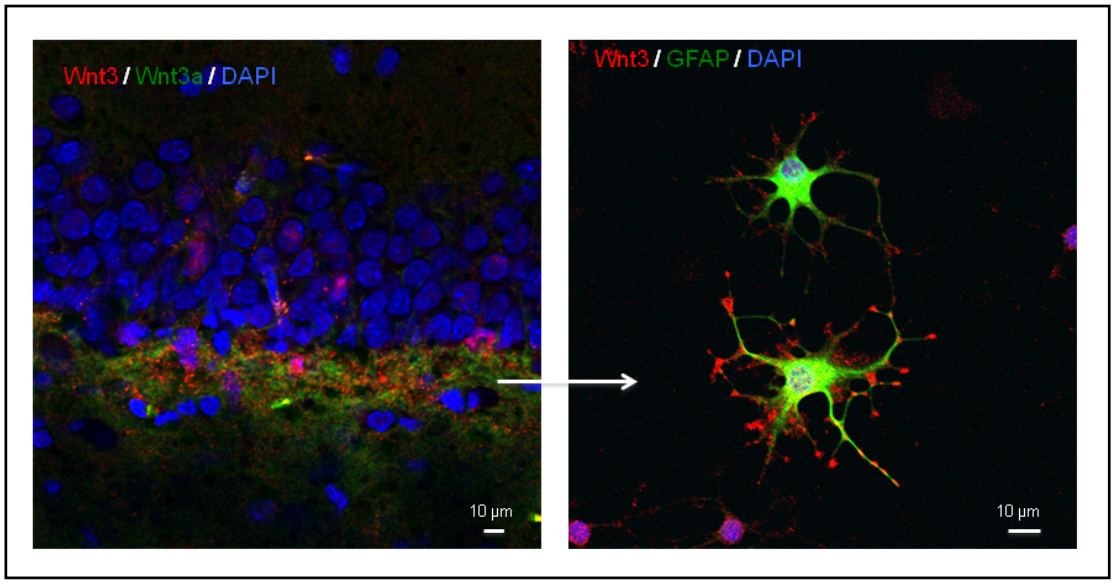

Fig.2 Wnt3/Wnt3a expressing astrocytes in adult hippocampal dentate gyrus (left) and the established primary culture in vitro (right)

Prepared primary astrocytes from young adult rats (7-8 weeks old) effectively express Wnt3 factors *in vitro* (right).

of "neurogenesis", in which nerve cells are routinely newly generated, in the hippocampus, which plays an important role in "memory and learning" functions in the adult brain. The sources of the neurogenesis,"adult neural stem cells", are present in the hippocampal dentate gyrus, which is the spatial recognition and memory center, and they self-renew by continually dividing, as well as differentiate into nerve cells and glial cells (astrocytes, oligodendrocytes)[19]. Adult neural stem cells were also shown to be present in the subventricular zone and olfactory bulb in addition to the hippocampus, and to continuously generate new nervous system cells and maintain the function of various regions of the nervous system[20-30].

When the fact that neurogenesis by adult neural stem cells plays an important role in maintaining the structure and function of the brain was demonstrated experimentally, it also opened up the possibility of making dramatic advances in basic research to analyze the regulatory mechanisms of adult neural stem cell themselves and to use neural stem cells as a means of treating neurological diseases[31-37], which until that time had been considered absolutely impossible. Moreover, it was also shown that the voluntary physical exercise (wheel running etc) and environmental enrichment both stimulate adult neurogenesis[38-41].

Activation of adult neural stem cells: Probing dependence on the environment

Does the fact that the phenomenon of "neurogenesis" in the brain is activated by stimulation, such as the quality or changes in an individual's environment, exercise, such as running, etc., mean that there might be changes in the adult stem cells themselves? The numbers of adult neural stem cells in the brain have been found to vary significantly with senescence. Aging is associated with a decline in the number of neural stem cells in the hippocampus[42-46], and as their number declines, there is a simultaneous decline in their capacity for "neurogenesis", i.e., to generate a wide variety of subtype neurons. Moreover, the number of adult neural stem cells changes with the individual's environment, such as stress or disease[47-49]. The phenomenon of neurogenesis in the hippocampus decreases even more markedly in neurodegenerative diseases and psychiatric disorders such as Alzheimer's disease, dementia, and depression. So, then, will transplantation therapy from outside to supplement the reduced number of "adult neural stem cells" itself become a direct and effective treatment? Actually, it will not.

The fact that the expression profile of neuronal and stem cells and large numbers of genes in hippocampus or other neurogenic region flexibly change in various ways as a result of exercise, changes in the environment, experience,

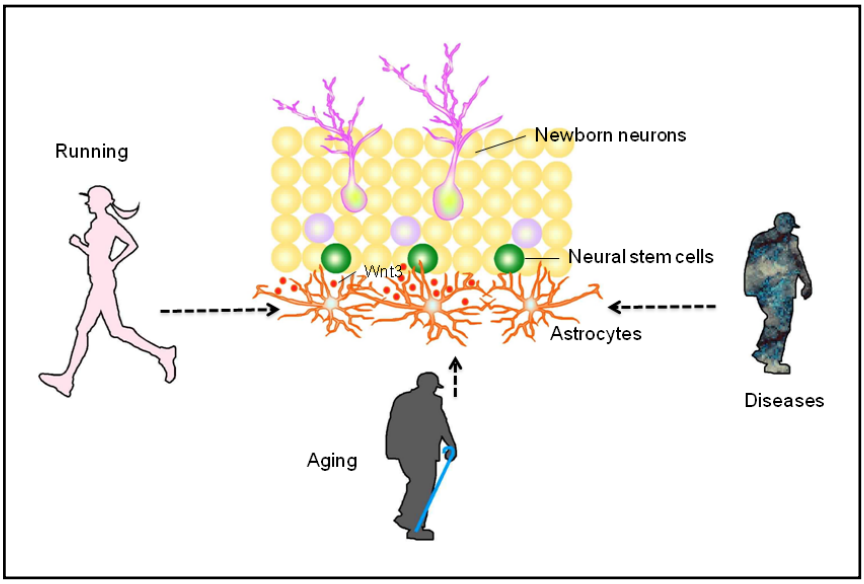

Fig.3 Environmental effects and adult neurogenesis

Astrocytes control adult neurogenesis sensitively from neural stem cells as their niches by secreting neurogenic Wnt3 factors in paracrine manner depending on the changes in the life (ex. Stimulation such as exercise (running), aging and diseases).

learning, etc., shows that the phenomenon of "adult neurogenesis" in the brain is finely modulated by molecular mechanisms that can easily change in response to external stimuli and the individual's living environment. Based on the results of our research, when we established and cultured "adult neural stem cells" from the hippocampus of aged mice and young mice, we found that there were no major differences in the growth ability or gene expression profiles of the adult neural stem cells in the independent experimental environment *in vitro*[50]. By contrast, when we established and cultured "astrocytes", which are the niche that supports neural stem cells *in vivo*, from the hippocampus of aged mice and of young mice, we found that the ability of the astrocytes from the aged mice to produce Wnt3, which functions as a nutritional factor for neurogenesis[51-54], was much lower, about 1/30, in comparison with that of the astrocytes from the young mice[50].

When we applied a stimulus to this group of aged mice by having them briefly exercise (running) to a degree that would not cause stress, we found that there was a large increase in the ability of their hippocampal astrocytes to generate Wnt3 factors[50]. Thus, these findings suggested that the intrinsic capacity for neurogenesis of adult neural stem cells themselves may not be fundamentally impaired by aging either.

The primary cause of the age-related decrease in the number of newborn neurons produced in the brain has been thought to be the decrease in the number of neural stem cells from which nerves are generated. However, recent studies have shown that there is a factor in astrocytes-niches, but not in neural stem cells, which significantly affects neurogenesis, and this factor plays a role leading to the rejuvenation of neural stem cells.

There is a strong possibility that improving the development of drugs that activate the function of the niche cells surrounding adult stem cells will lead to activation of adult neural stem cells. Even in organs and tissues in which transplantation therapy and surgery is difficult, such as the brain, a way to elicit the latent potential of adult stem cells by molecularly identifying the control mechanism of resident adult stem cells and the interacting roles of surrounding cells without invading brain tissue has now become clearer. In particular, the fact that the phenomenon of neurogenesis in the brain is eventually rescued by individuals' activity, such as exercise/running, and by the external environment has made it possible to confirm the possibility of a method of achieving a synergistic effect by adding it to existing drug therapy and activating neural stem cells, even in neurodegenerative diseases and psychiatric/mental disorders, such as Alzheimer's disease, dementia, and depression.

Methods of utilizing effective neurological disease research using iPS cells

While it is possible to relatively easily extract and analyze adult stem cells from some of the organs and tissues in our bodies at living status, including viscera, such as the liver, and skin, fat, bone marrow, etc., it is extremely difficult to

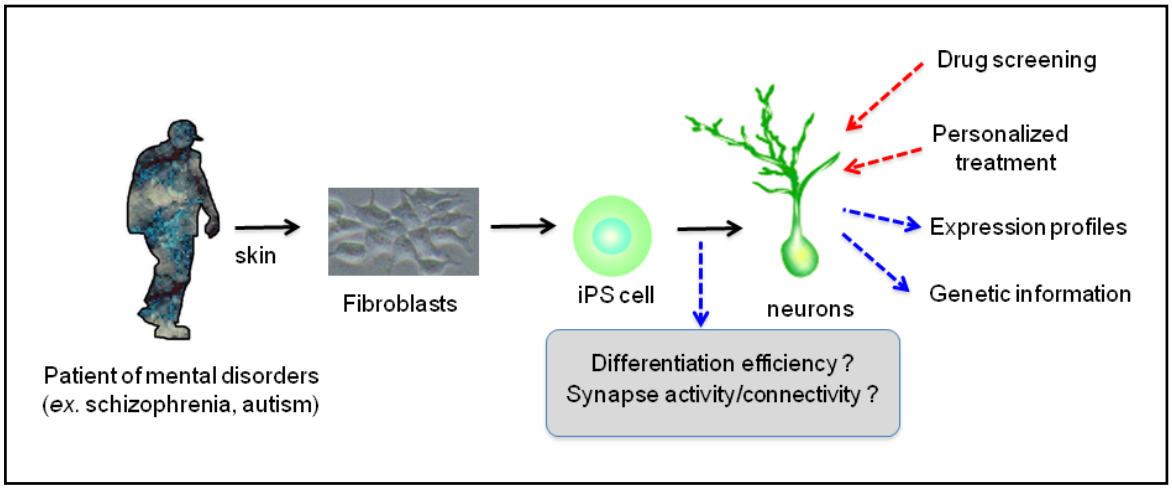

Fig.4 Induced pluripotent stem (iPS) cells from patients of mental disorders

Clinical neuroscientists have always been challenged by not having direct access to the organ of interest. Established iPS cells from patient's skin can re-consist the process to give rise to neurons in vitro. Clinical applications such as drug screening for personalized treatment may become available.

obtain neural stem cells/progenitors or biopsy material from the nervous tissue in the brain. It is certainly possible to perform research on basic molecular mechanisms by combining adult neural stem cell culture systems and animal experiments, but it is also no exaggeration to say that it is virtually impossible to actually analyze (living) adult neural stem cells in the brains of patients with psychiatric/mental disorders, or to analyze the processes, for example, by which differentiated neurons or glial functions and intercellular responses change and proceed to the malignant disease state. That is why it is usually necessary to conduct research by using postmortem brains as specimen material, and the result of that been that analyses of neurological diseases, and especially research on psychiatric/mental disorders, have hardly progressed at all, and they are still in a state of groping in the dark.

To break out of this situation, researchers vigorously pursued studies in which iPS cells from patients with a variety of neuropsychiatric/mental disorders are prepared, allowed to differentiate into neurons, and compared with neurons derived from iPS cells established from healthy human subjects. Instead of directly using iPS cells (derived cells) for transplantation, it is "modelling pathogenesis" (disease model reconstruction) study in which the functions of the molecules or genes that are the cause of the disease can be analyzed by a process in which iPS cells are induced to differentiate into component (stem) cells of organs that are difficult to access, such as the brain. Whether or not the causative genes that had been identified in previous animal-based studies actually contribute to functional abnormalities in neurons derived from human iPS in the disease has been investigated and confirmed, such as spinal muscular atrophy (SMA), familial dysautonomia (FD), and Rett syndrome (RTT). As in these three research examples, when a single causative gene has already been proposed on the basis of previous research, and when symptoms are manifested relatively early stage, such as in newborn infants, there is the advantage to detect the abnormalities efficiently, and application to various similar diseases will be possible in the near future.

There was even a recent report that it had become possible to detect abnormalities based on the study of "disease model reconstruction" using iPS cells in mental disorders, whose onset, as in schizophrenia (SZ)[58], often occurs in the period between puberty and young adulthood and whose causative gene is still unclear. When neurons were transformed from patients-specific iPS cells in the culture dish, the patient-iPS-derived neurons made fewer connections, or synapses, with other neurons from people without mental disorders[58]. A mitigating/repairing effect on patient-iPS-derived neurons was actually seen when clinical reagents for SZ patients were added in the culture dish[58].

It appears that, if these experimental systems are used, besides being able to apply them to drug discovery screen-

ing even in cells that are components of human tissues that are difficult to access, they will make it possible to provide "order-made treatment," in which treatments for diseases that are adapted to differences in the genetic environment and growth environment of each individual are discovered based on iPS-based "modeling pathogenesis" studies for each individual patient.

Activating the latent potential of stem cells

The essence of regenerative medicine lies in reproducing the functions of tissues *in vivo* that have been lost as a result of disease or injury. If we focus our attention on tissue and organ regeneration, at first glance a method that "replenishes" the stem cells that compose tissues appears to be the shortest way to restore lost functions. In reality, however, in many cases it is difficult to impose the physically major procedure of "transplantation surgery" on the ailing patient. There are also many hurdles that should be overcome, i.e., whether the cells for transplantation that have been prepared will efficiently survive in the affected region, whether they will adapt well to the cellular network that compose the function of the tissue, and whether their homeostatic properties can be secured without losing their self-renewal ability and multipotentiality. We think that a great deal of academic basic research on the stem cell components of each tissue, including on the extracellular environment, response mechanisms, role of niches, and exploration of their potential, as well as on various stem cells themselves, is still needed. It seems that pursuing basic research more deeply will be of significance in discovering more efficient new regenerative medicine techniques in the future.

Induced cells derived from iPS cells have the advantage of higher growth rates and being easier to prepare in large quantities in comparison with the process of establishing and culturing the adult stem cells present in small numbers in adult tissues. However, the same as in ES-cell-derived regenerative medicine research cases, iPS cells retain many embryonic stem cell properties, and without conditioning to the "adult" environment, they involve unknown risks of causing abnormal growth or carcinogenesis in the future. As stated above, we think that regenerative medicine research methods that use iPS cells to reconstruct the patient's diseased tissue outside the body, create a cell model of the patient's own disease, and utilize it for assessment and detection of drug discovery and treatment cases is highly rational. In terms of stem cell regenerative medicine, it is important to "activate" the adult stem cells present in one's own body more safely and in a way that is closer to nature.

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