Neural Stem Cells and

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Aging is usually associated with progressive loss of central nervous system functions particularly in the presence of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. In the last few years, cell replacement strategies have been put forward in order to repair the brain and replace the lost brain tissue due to disease. However, successful application of such therapies require the full understanding and knowledge of the complex relationships involved between neural stem cells, normal aging and the neuropathology involved.

The human brain has the ability to retain normal function for a considerable number of years. However, the emergence of neurodegenerative disorders associated with old age is becoming increasingly common. For example, the prevalence of Alzheimer's disease increases from 2-3% in individuals having 65 years of age to around 40-45% in those over the age of 85 years.[1] The sharp rise in life expectancy in many developed and developing countries not only leads to the explosive growth in the numbers and proportion of older persons but also in the incidence of neurodegenerative disorders associated with age. It is therefore not surprising that a lot of attention has been devoted to the recent advances in stem cell therapies which can offer the potential of replacing brain cells in the aging and diseased brain.

The Aging Brain

Similarly to other organs, the brain undergoes a progressive decline in function with increasing age.[2] In the central nervous system, normal aging (in the absence of any neuropathology) is associated with altered structural changes. The number of brain cells decreases in many areas of the brain and post-mortem studies indicate a reduction of around 5% in brain volume per decade after the age of 40 years.[3] There is also an increase in the size of the ventricles, shrinkage of several brain areas such as the frontal cortex and the striatum, and loss in the number of synapses, especially in the prefrontal cortex. On a cellular level, aging of the central nervous system is accompanied by a number of changes that impair cellular function. Oxidative stress increases, damage to both DNA and protein accumulates, cellular metabolism is impaired and lipid and protein by-products accumulate in the brain.[4] Mitochondrial function also declines, with an associated increase in mitochondrial DNA oxidation and impairment of DNA repair.[5] A significant number of signal transduction pathways are also altered, leading to reduced efficiency in neurotransmitter release. Although these changes per se do not cause neurodegeneration, they may predispose the brain to pathologies such as Alzheimer's and Parkinson's diseases.

One of the most remarkable changes that occur in the brain is the alteration in cognitive performance. Compared to young individuals, older adults show different patterns of brain activation when performing cognitive tasks. Most notably, there is age-related impairment in short-term memory and cellular repair capacity, with the latter mostly evident in the presence of neurodegenerative disease.

Age-related Neuropathology

Three of the most prevalent age-related neurodegenerative disorders are Alzheimer's disease, Parkinson's disease and stroke. All three share a common feature: specific populations of brain cells are affected. In Alzheimer's disease, a disorder which mainly affects memory and cognitive function, the brain regions mostly affected are the hippocampus and the cerebral cortex. In Parkinson's disease, a disorder associated with loss of motor function, there is selective loss of dopamine-producing cells in the substantia nigra. In stroke, characterised by blockage or rupture of a blood vessel, there is selective loss of brain cells in the area supplied by the damaged blood vessel. Traditional therapies for each of these diseases have focused on pharmacological approaches. Because in Alzheimer's disease there is loss of cholinergic function, pharmacological agents that have been developed sought to enhance cholinergic transmission via the inactivation of enzymes that break down acetylcholine.[6] In Parkinson's disease, therapeutic agents aim to enhance dopaminergic transmission by increasing the levels of its precursor, L-DOPA, or by blocking enzymes responsible for its breakdown or else by direct stimulation of dopamine receptors.[7] In stroke, treatment is usually directed towards minimising the secondary damage that follows injury.

Neural Stem Cells

Recent studies have shown that certain areas of the brain are capable of producing new cells, a process known as neurogenesis. During the course of neural development, there is a progressive restriction in the differentiation capacities of the cell. Therefore, embryonic stem cells have pluripotent characteristics (ability to develop in almost all kinds of cells) whereas tissue stem cells have multipotent characteristics and only differentiate into a subset of cells related to the tissue in which they are present. Neural stem cells can only give rise to three major types of cells in the central nervous system: neurons, astroglia and oligodendrocytes. Under normal conditions, there are several possible outcomes for a neural stem cell. Stem cells may remain quiescent and not undergo division, or may undergo apotosis and cease to exist. Alternatively, stem cells may proliferate to produce new stem cells or else differentiate into a mature brain cell. This outcome is regulated by a variety of factors such as growth factors, receptor expression and neurotrophic factors.

Role of Neural Stem Cells in the Aging Brain

In the adult mammalian brain, neural stems cells are located in two major areas of the brain: the olfactory bulb and the hippocampus. Studies show that age-induced stress factors such as an increase in oxidative stress and DNA damage inhibit the formation of neural stem cells. This is most evident during development. For example, prenatal stress inhibits neurogenesis and affects learning and memory in

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the adult hippocampus.[8] Other factors have been found to have a profound effect on neurogenesis including the presence of an enriched environment, exercise, ischemia and antidepressant drug therapy. Neurogenesis also decreases with age even in the absence of any neurodegenerative condition. This is mostly evident in the hippocampus.[9] Neural stems cells may also have a role in age-related diseases of the brain. Amyloid plaques, which play an important role in the pathology of Alzheimer's disease, not only inhibit the proliferation of neural stem cells but also promote apoptotic cell death. Individuals with early-onset Alzheimer disease (of which a genetic component is the main contributor) exhibit as much as 75% loss of neurons in the olfactory bulb leading to a significant loss of smell.[10] A decrease in the proliferation of neural stem cells in the hippocampus may also contribute to the pathology of Alzheimer's disease and the associated loss of cognitive functions.

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