Effect of ageing on neural stem cells (nscs)

Neural stem cells(NSCs) are multipotent, self-renewing cells that can generate the typicalphenotypesof thenervous system. NSCs are produced throughout the life of an adult via the process known to be asneurogenesis. Like other tissue-specific stem cells, NSCs persists as separate small and discrete populations in the brain and can undergo extensive proliferation giving rise to new glia and neurons. In mammals they persist throughout the entire life and play the important role of continuously renewing neurons. Upon receiving exogenous stimuli from the environment stem cells differentiate into multiple cell types and undergo a form of asymmetric cell division to generate two daughter cells, one specialized and the other one non-specialized. NSCs mainly differentiate intoneurons, oligodendrocytes and astrocytes. NSCs are viewed as adult stem cells due to their restricted ability to differentiate. NSCs within the CNS mainly differentiate to replace lost or danaged neurons or in some casesglial cells. NSCs differentiate into new neurons in the dentate gyrusof thehippocampus as well as the Sub Venticular Zone of lateral ventricles, which is a remnant of the embryonic germinalneuroepithelium.

NSCsin adult brain

Adult NSCs were first isolated from mouse striatum in the early 1990s. They are capable of forming multipotent neurospheres when cultured *in vitro* . Neurospherescan produce self-renewing and proliferating specialized cells. The neurospheres can differentiate specifically to produce the specified neurons, oligodendrocytes and glial cells. NSCs are stimulated to begin differentiation via exogenous signals from the stem cell niche or microenvironment. The capability of the Neural Stem Cells to replenish

damaged or lost neural cells is calledneurogenesis. Neurogenesis in the adult mammalian Central Nervous System is restricted only to a few regions. New neurons basically arise in the subgranular layer (SGL) of the hippocampal dentate gyrus and in the subventricular zone (SVZ) of the lateral ventricle. A large number of neuronal precursor cells present in the SVZ migrate to the olfactory bulb and there they constantly replace interneurons . In addition the SVZ also serves as a constant source for glial cells. The Ependymal cells seem to play an important role in adult neurogenesis. The astrocytes of the SVZ produce neurogenesis inhibitor BMPs which are in turn neutralized by noggin that is produced by ependymal cells. Thus the formation and maintenance of this neurogenic region is obviously dependent largely on the interaction between the SVZ astrocytes and the ependymal cells. The glial tubes produced by the astrocytes and the ependymal cells are used by migratingneuroblasts. The astrocytes in the tubes helps to provide support to the migrating cells as well as insulation from chemical and electrical signals released from surrounding cells. The astrocytes also functions as the precursors for rapid cell amplification. The dentate gyrus NSCs produce excitatory granule neurons that are involved in learning and memory while the neuroblasts form tight chains and migrate towards the specified site of injury or damage to replace or repair neural cells.

Complexity of Neural Stem Cell Niche

In the adult mammalian brain the neural stem cells persist in a typical neurogenic niche known as the subventricular zone (SVZ). SVZ neural stem cells (NSCs) are self-renewing and multipotent in culture. In rodents, the adult NSCs correspond to SVZ astrocytes (type B cells) which are derived

from radial glia. Type B cells again generate transit-amplifying (type C) cells which then give rise to more young neurons (type A cells) and oligodendrocytes. Young neurons are born throughout the adult neurogenic niche and migrate tangentially through a complex network of chains that merge into the rostral migratory stream (RMS), a major pathway that leads into the olfactory bulb (OB). Within the OB, young neurons differentiate into multiple types of interneurons. The SVZ was thought to be limited to the lateral wall of the lateral ventricle, but recent work shows that the adult neurogenic niche is significantly more extensive and includes portions of the medial and dorsal walls of the lateral ventricle and the RMS itself. Furthermore, several recent studies explain why young OB neurons are generated in such an extensive region. Type B cells in different regions of the SVZ, although able to self-renew and generate neurons and glial cells in vitro, are heterogeneous and committed to producing defined neuronal subtypes in vivo. The adult SVZ therefore provides a rich system to study not only neural replacement, but also the cellular and molecular mechanisms underlying regionalization and cell-fate specification. It is hypothesized that neurogenesis in the adult brain originates from NSCs. The origin and identity of NSCs in the adult brain remain to be defined. The most widely accepted model of an adult NSC is a radial, astrocytes-like, GFAP-positive cell. Quiescent stem cells are Type B that are able to remain in the quiescent state due to the renewable tissue provided by the specific niches composed of blood vessels, astrocytes, microglia, ependymal cells, and extracellular matrix present within the brain. These niches provide nourishment, structural support, and protection for the stem cells until they are activated by external stimuli. Once activated, the Type B cells develop into Type C

cells, active proliferating intermediate cells, which then divide into neuroblasts consisting of Type A cells. The undifferentiated neuroblasts form chains that migrate and develop into mature neurons. In the olfactory bulb, they mature into GABAergic granule neurons, while in the hippocampus they mature into dentate granule cells. NSCs have an important role during development producing the enormous diversity of neurons, astrocytes and oligodendrocytes in the developing CNS. They also have important role in adult animals, for instance in learning and hippocampal plasticity in the adult mice in addition to supplying neurons to the olfactory bulb in mice.

NSC progenitors

Most NSC progenitors produce are sel renewing clones of solely neurons, others of solely glia, but, most interestingly, there exists a small subset of progenitors that has a large proliferative potential and unquestionably produces both neuronal and glial progeny. Thus all these simultaneous discoveries in support with the cardinal property of NSCs led to the idea that the development of both central and peripheral nervous system like blood circulatory system relied on the existence of multipotent adult stem cells which repeatedly produces restricted neural progenitors that further divides for just a few times and produces small number of totally differentiated progeny. Neural progenitor cells (NPCs) are further classified into two basic types: multipotent NSCs and Intermediate progenitor cells (IPCs). or transit amplifying progenitor cells.

NSCs in Aging and Diseases–a tool for neurotherapy?

Neural stem cell proliferation declines withaging. Various approaches have been elucidated to counteract this age-related decline. As FOXO proteinsregulate neural stem cellhomeostasis, FOXO proteins have been used to protect neural stem cells by inhibitingWnt signaling. Epidermal growth factor(EGF) andfibroblast growth factor(FGF) aremitogensthat promote neural progenitor and stem cell growth *in vitro* , though other factors synthesized by the neural progenitor and stem cell populations are also required for optimal growth. The role of NSCs duringstroke, multiple sclerosis, andParkinson’s disease is currently being elucidated in animal models and humans and these investigations is supposed to implicate tremendous therapeutic value in the field of regenerative medicine. Many classical experiments have shown that NSCs are engaged in the migration and replenishment of dying neurons in adult brain at site of injury. Chemokines such asSDF-1areleased during injury were responsible for the directed migration of human and mouse NSCs to areas of injury. All these results have been widely reproduced and expanded by investigators while visualizing neurogenesis during development, and neurogenesis in the adult as evidence of the responses of adult NSCs activities and neurogenesis during homeostasisand injury. Cell death is a major characteristic of all acute disorders related to CNS as well as various other neurodegenerative diseases. The severity of these diseases characterized by loss of neurons and other associated cells are amplified as CNS lack regenerative abilities for whole cell replacement and damage repair. One way to outwit this critical challenge is to use cell replacement therapy involving regenerative NSCs. NSCs can be efficiently cultured *in vitro* as neurospheres. These neurospheres are composed of NSCs and progenitors (NSPCs) along with EGF

and FGF growth factors. The withdrawal of any of these growth factors tends to activate differentiation into neurons, oligodendrocytes and astrocytes, which can then be transplanted within the brain at the specific site of injury. This therapeutic approach has been examined inmany neurodegenerative diseases including Huntington’s disease, Parkinson’s disease andmultiple sclerosis where it proved to be excitingly beneficial. NSPCs induce the characteristic neural repair via intrinsic properties ofimmunomodulation and neuroprotection. The possible routes of NSPC transplantation include xenotransplantation and intracerebral transplantation. Another alternative therapeutic approach to the transplantation of NSPCs is by pharmacologicaly activating the endogenous NSPCs (eNSPCs). Activated eNSPCs produce neurotrophic factors and several treatments that activates a pathway involving the phosphorylation of STAT3 on the serine residue and the subsequent elevation of Hes3 expression (STAT3-Ser/Hes3 Signaling Axis) oppose neuronal death and disease progression in models of neurological disorder.