

## Neural Stem cells: Several Methodology in Regenerative Medicine to Cure Brain Injury

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### Abstract

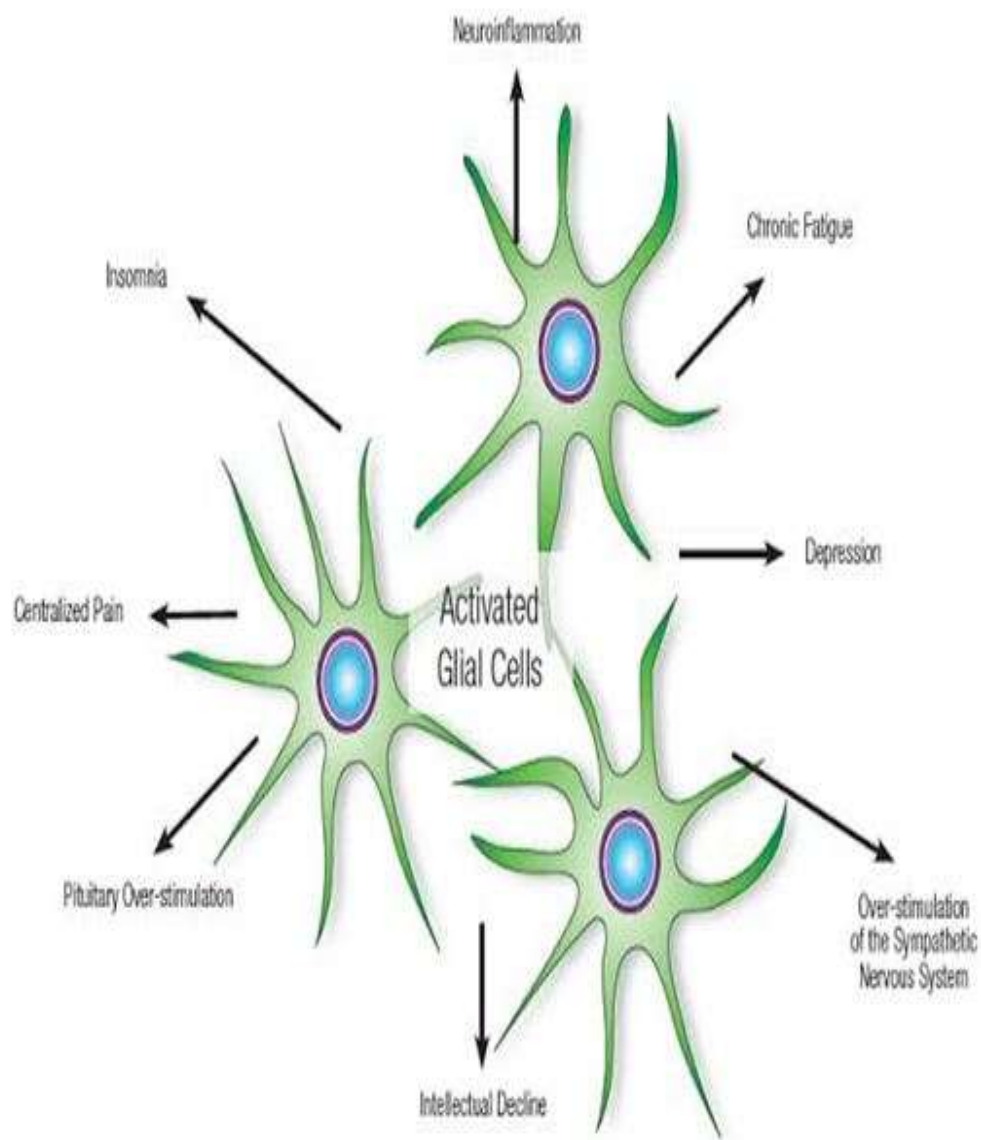
The specific set of cells from stem cells is a scientific miracle. These stem cells help in rebuilding damaged and diseased tissues, and also help in formation of any type of cells. One type of stem cell called Mesenchymal stem cells (MSC) has the ability to differentiate into non lineage cells namely glia and neural stem cells. Several research indicates neural mechanism for neuroglia has its specification. These neural mechanism show interconnected components of cell signalling. Furthermore they highlight the signalling pathways inside neurons. Most dependent cells of these pathways are ligands and cellular architecture flowing on these ligands. The limit to understanding this architecture ends with neurosphere, spheroid structure and organoids. Sometimes injuries in brain are devastating and there is no cure in sight. The symptoms also show complications in neural regeneration. Local environment factors effects loss of neurons. This review focuses more on therapeutic solutions to cure damaged neurons and give more attention to glial cells. The regeneration of stem cells in its various forms are now put to effective use for both neuroglia and neuronal replacements.

### Keywords

Glial cells; Neural stem cells; Nerve cells

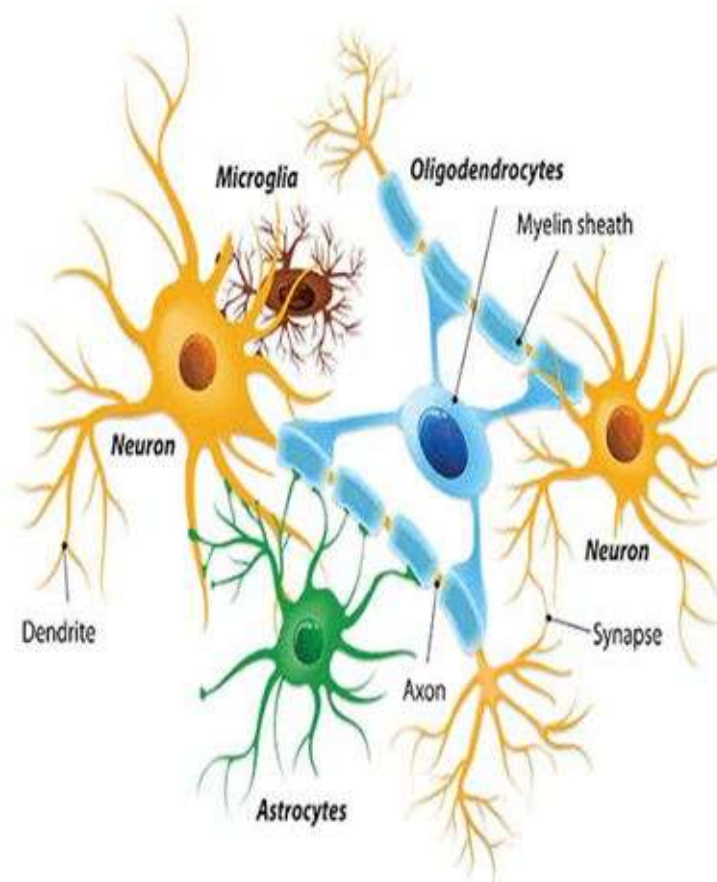
## Introduction

Glial cells are present in large numbers in the central nervous system (CNS), they help in maintaining balance, forming myelin, and provides support and protection to neurons. There has been a significant progress in glial formation and repair, stem cells provides valuable solution to the problem [1] (Figure 1).



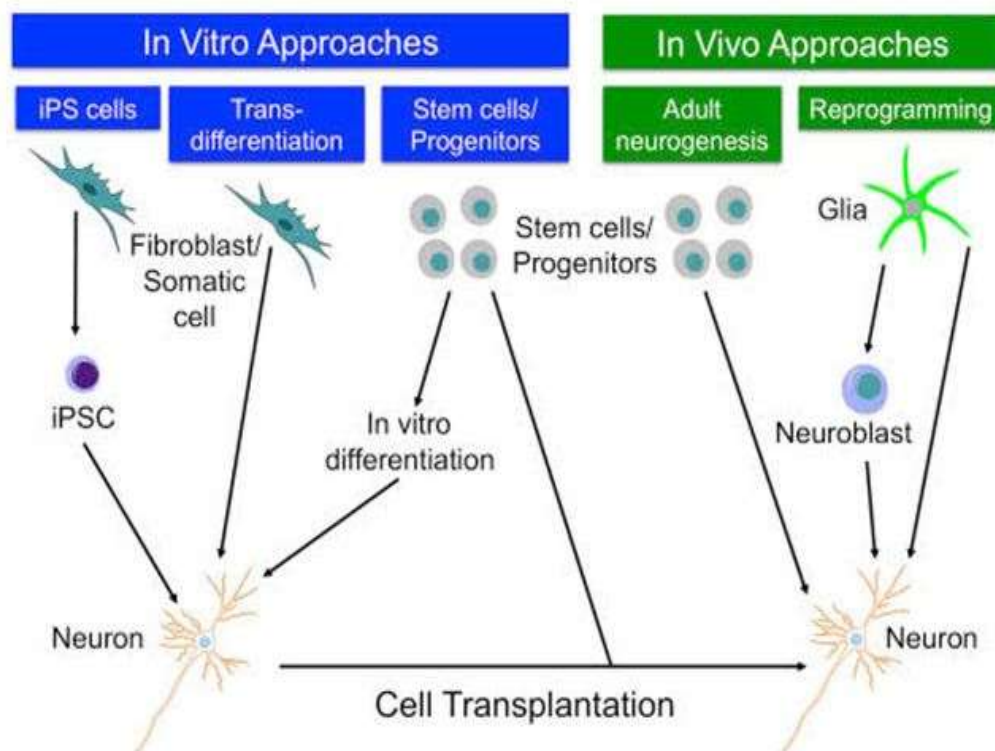
**Figure 1:** Shows the glial cells structure during activation [2].

There are three different types of glial cells. The astrocytes, oligodendrocytes and microglia [3] (Figure 2)



**Figure 2:** Shows the glial cells and its types [3].

It is important to understand glial cells in order to solve the neurological disease [4]. MSCs have potential ability to help in neural cells formation. But majority of tests have proved iPSC (induced human pluripotent stem cells ) have the capacity to generate glial cells and neural stem cells [5]. Neurons have unique characteristics to communicate via chemical synapsis. Glial cells clean up after this mess, the task peculiar to the star shaped astrocytes [6]. Glial cells thereafter communicate through non lineage cells, called synaptic communication. The components of synaptic cells form the target organ in the periphery such as muscle cells and glial part[7]. The glial part forms the entire synapse involving perineural nets which is densely arranged extracellular matrix firmly holding the synapse. There is consistence in the multiple role of glial cells, thus increasing in number of these cells outnumbering neurons. They also act as oligodendrite progenitor cells in brain cells proliferation[8]. This is the immature step of neural generation. Why it is called immature is because of one sided support to progenitor cells division. The cell NG2 glia has three purpose, one to hold the progenitors and others synapsis. An intriguing question is, the pro-genesis is remodelling of synaptic connections of glia that contributes to the performance of astrocytes in formation of nerve cells [9] (Figure 3).

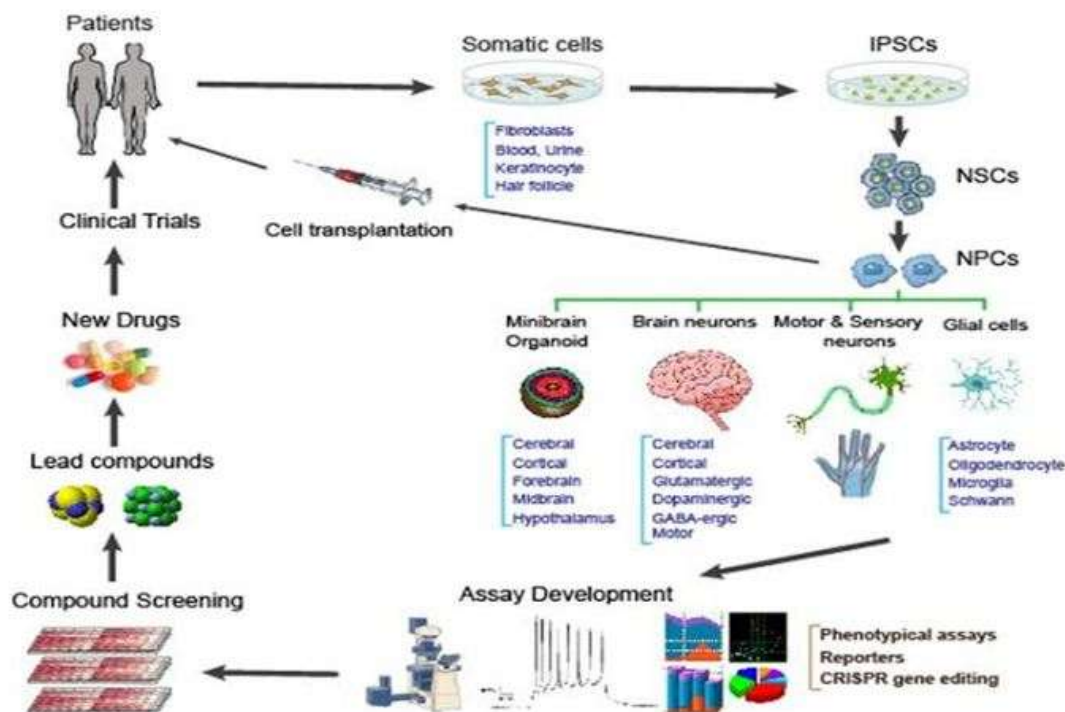


**Figure 3:** Shows glia cells and its division into neural cells [10].

This review has lot of queries answered on role of glial cells in development of brain, glial cells act as progenitor, evidence of radial glia cells, glial cells and CNS and emergence of progenitors [11].

### Stem Cells Prominence

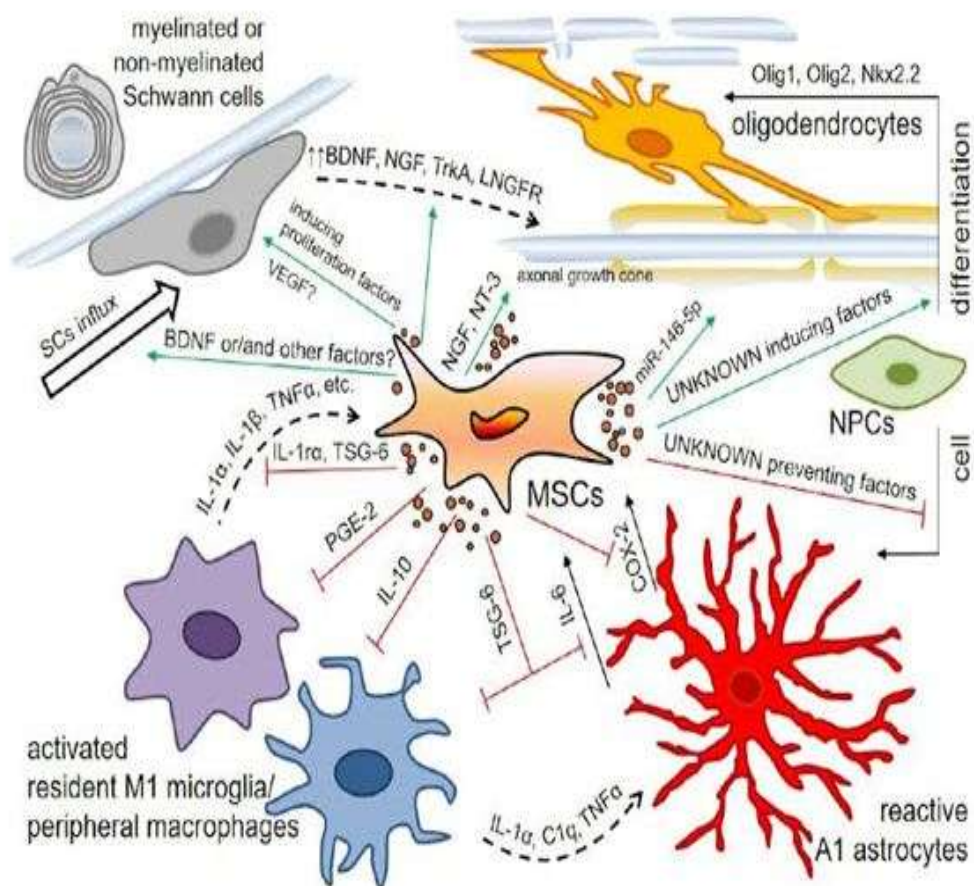
The most prominent role of glial cells is structure maintenance and bonding. The term nerve cement was promulgated a century ago and neuroglia arrived from that. Glial cells play almost all the role in brain including CNS functions, development, injury and curing diseases [12]. With knowledge of glial cell types, NG2-glia or polydendrocytes had been identified as oligodendrocyte progenitor cells. In addition there are few other glia cells such as Muller glia in retina and Bergmann glia in cerebellum [13] (Figure 4). Several studies have suggested that human neurogenesis is different from rodent [14]. Due to differences in neuroanatomy, profound results are inadequate to cure human cells. Hence the concept called iHPSC was discovered. Induced Human pluripotent stem(iHPSC) cells is an in-vitro success in curing brain injury[15]. It has been a valuable tool for modelling diseases, mapping development of CNS and treasuring the CNS cures. iHPSCs were derived from transcriptional factors of cells. They can be obtained in large numbers from human blood cells, skin fibroblasts and somatic cells [16].



**Figure 4:** Suggests the iPSCs method of drug development for brain cure.

They are the solution to formation of neural cells which helps on replacing damaged tissues and cells. However there are hurdles to this formation. It is the microenvironment that prevents or rather restricts the formation of neural cells [17]. The balance of microenvironment is crucial for regeneration of brain cells. Glial cells volunteers to maintain the homeostasis of microenvironment. The communication between glial cells and neural cells is important for regeneration. Stem cells are blessed with characteristics for formation of any cell or any bodily organ [18]. Neural stem cells already present in subventricular region generates new neurons, some present in hippocampus region generate astroglia. Since these neural stem cells has limited capacity to produce glial cells, stem cells is often the best alternate during disease and damage [19].

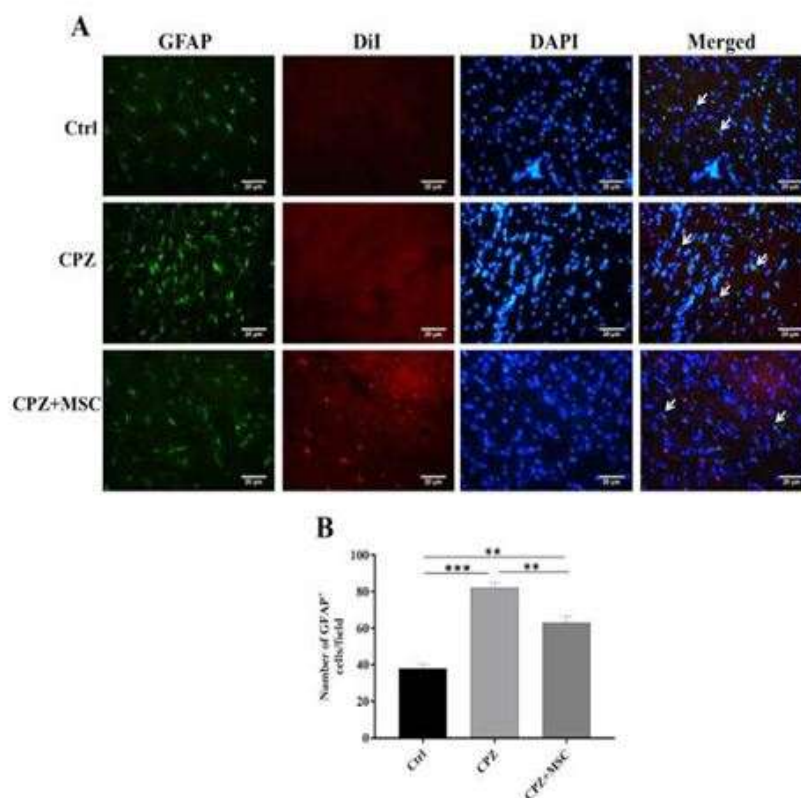
Adult stem cells from mesoderm layer differentiate into neuron and glial cells under the influence of growth inducers. MSCs differentiation helps in neuron functions and also glial cells transformation for regeneration therapies. Many studies have suggested that MSCs help in treatment of several brain injuries including Alzheimers, Amyotrophic lateral sclerosis, cerebral palsy and Parkinsons diseases. These cells have the ability to exert paracrine effects inducing protein in impaired glia for repair [19-21] (Figure 5).



**Figure 5:** Shows MSC in neural environment [20].

### MSC plays an effective role in neural cells

MSCs are abundant in the adipose tissues but have less significance in placenta. They harvest less; hence biological and chemical inducers are used to derive MSC from bone marrow. The results have shown these derived MSC has better regeneration capacity in animal model [22] (Figure 6). MSC are successfully obtained by adjusting the cell culture and use growth hormones for neural differentiation. The changes in components are observed through cell conditions in brain, absorption and secretion of components by various inducers [23].

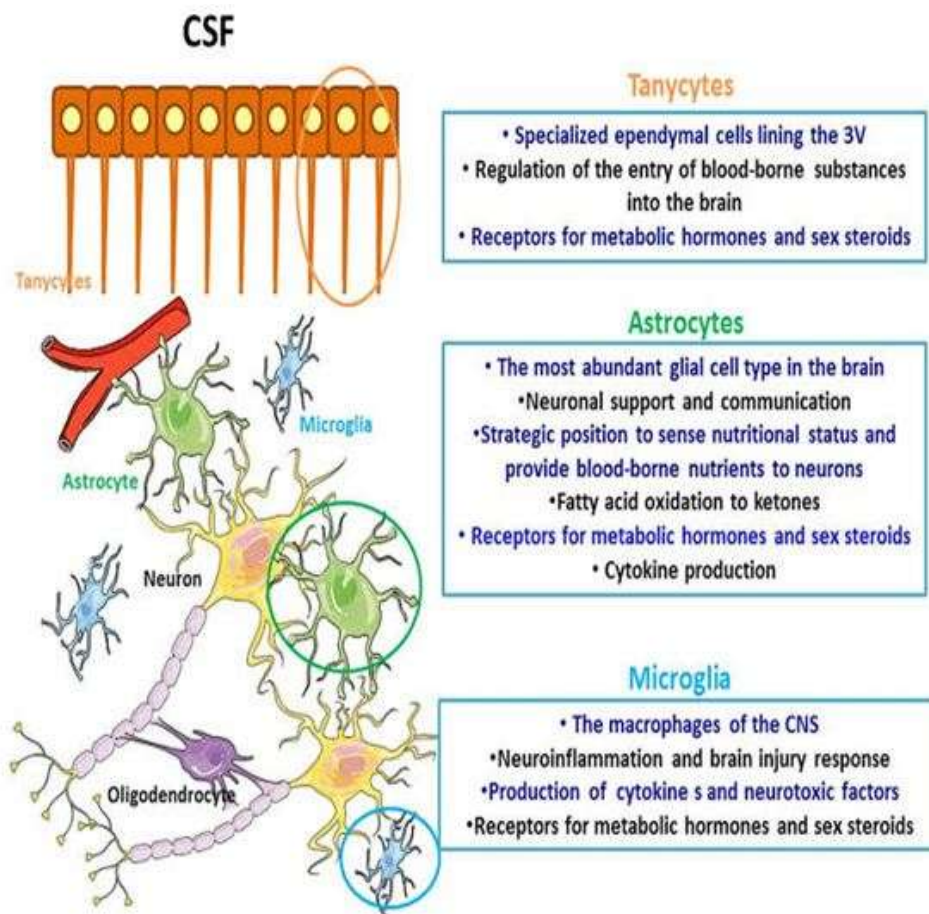


**Figure 6:** Shows presence of MSC in glial cell [22].

### Glial Cells Role Play in Brain

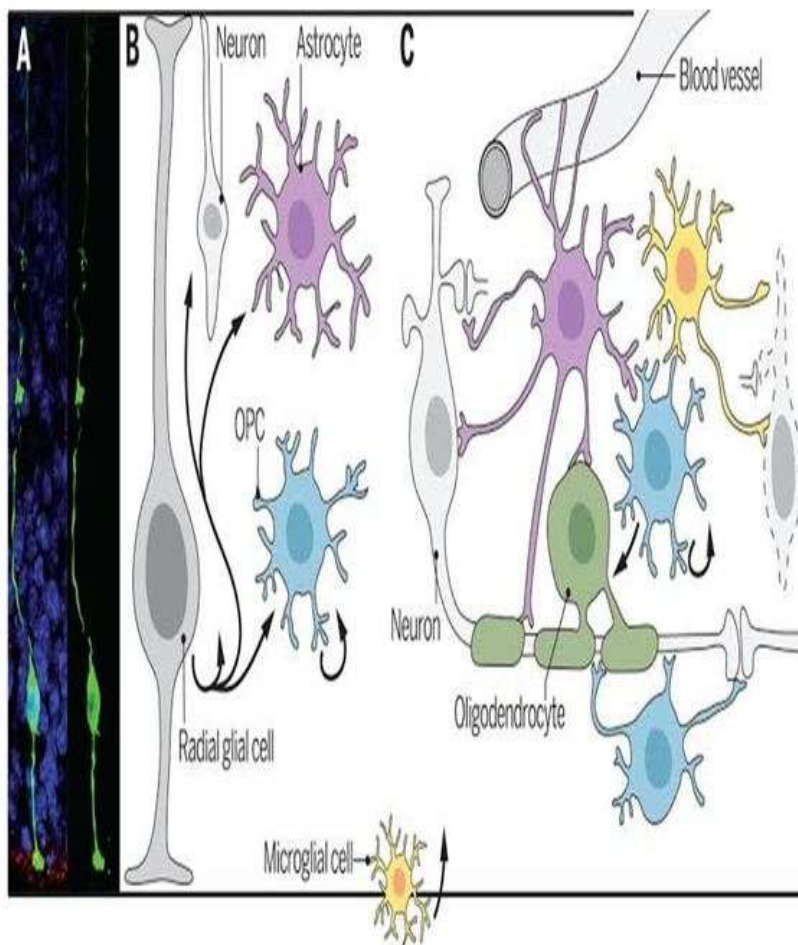
As per knowledge glial cell types have been playing a part in nerve regeneration. Main part of brain is the CNS which contains the grey matter and white matter [24]. Astrocytes of glial cells are abundant in them. They act as support for neurons and play a part in homeostasis. Astrocytes also harbour receptors and transporters which is the main role of homeostasis. The surface contains K<sup>+</sup> channel, helps in regulating potassium levels and aquaporin receptors regulated osmosis changes. Astrocytes interlinks gap junctions due to presence of glucose receptors, glutamate, glutamate aspartate and glutamate transporter 1. Calcium is the one transported into these gaps to release the neurotransmitters from astrocytes [25]. Hence it is called gliotransmission. This transmission plays a crucial in receiving inputs from neurons. The biochemical support for blood brain barrier and ion balance are done by astrocytes. After the brain injury, the signalling pathways are activated by the reactive astrocytes. Glial scar formation might stop axonal growth, inhibiting factor interleukins produced by the astrocytes protects the neurons. Hence there is a dynamic signalling taking place in the inflammatory function and produces notch in the pathway modulating the axon growth [26]. The myelinating cells in white matter and grey matter in CNS is the oligodendrocytes. Myelin sheets plays effective role in axon survival and are believed to regulate environment where neurons are present. Basically both oligodendrocytes and neurons play mutual role. Former provides structural and neuroprotection to axons and latter provides maturation to oligodeendrocytes [27]. Nerve glial antigen 2 cells help in co-localising oligodendrocyte

precursor cells. They contain dividing cells in high numbers which expresses ion channels and conduct electric current. They have self-propagating ability and differentiate into oligodendrocyte cells, potentially useful for cellular therapy of brain injury [28] (Figure 6,7).



**Figure 6:** Shows the work of glial cells in brain [28].

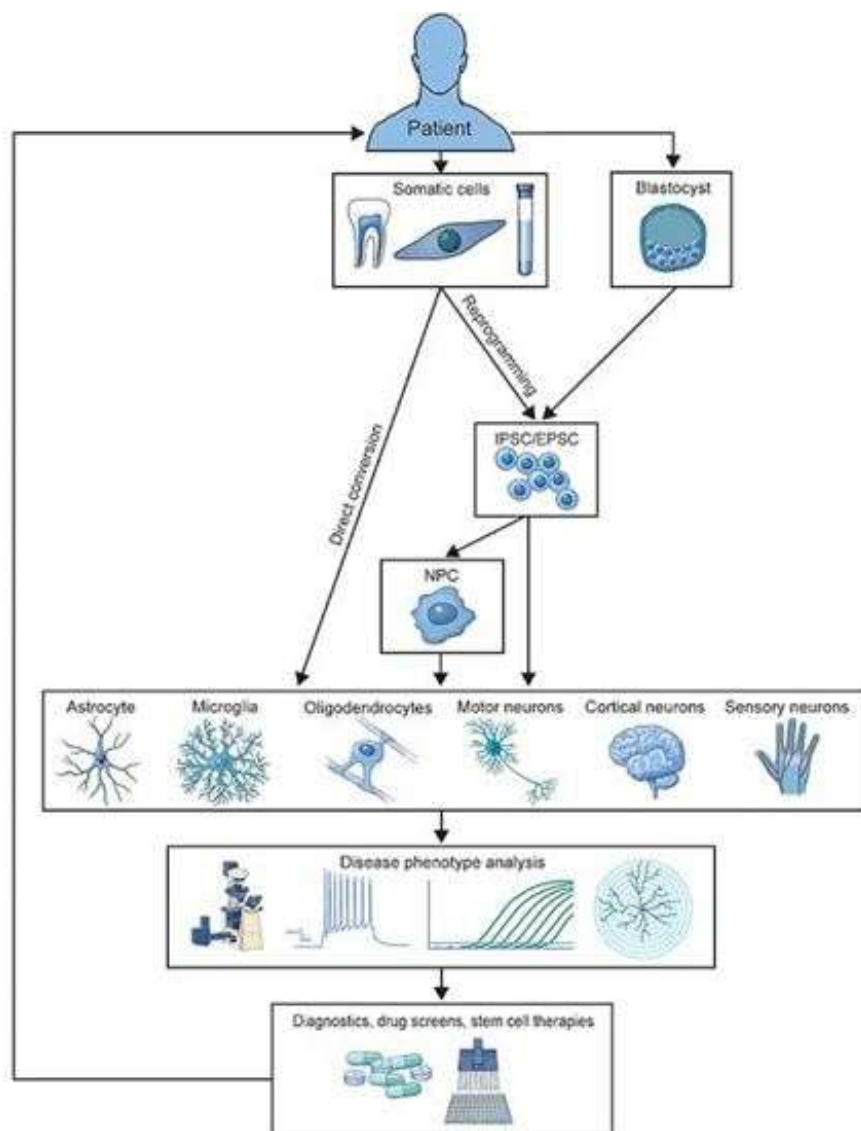




**Figure 7:** Shows environment of glial cells in CNS [29].

### Stem Cells and Neurogenesis

During neurogenesis, macroglia containing astrocytes and oligodendrocytes undergo asymmetric division to form glial-restricted progenitors [30] (Figure 8).



**Figure 8:** Explains the process for stem cell therapy for brain injury [30].

### Stem Cells and its Benefit

Stem cells have not reached its full potential in treatment of nervous system. Most fascinating studies often establish greater results, such fascination is the stem cell treatment of nervous cells [31]. The animal models often expedite clinical trials resulting in compounding results. They help in determining the site delivery, dosage, transplantation time and safety of the experiments. Most specific of them all are the cell types to choose from, either ESC, NSC OR iPHSC [32]. But the source basically varies from each cell type. Bone marrow tailor made to suit the cells to form organs. More often fetal cells are more preferred than adult cells. Imaging techniques have helped in tracking the cells, most common used are magnetic imaging resonance, positron emission tomography and bioluminescence [33]. The most common problem of regeneration is the rejection of graft cells. But the for rejection solution lies in stem cells itself, induced pluripotent stem cells are used, giving an edge over ethical issues. Future studies can

all underline the genetic profile of diseased cells and carve a necessary cell to treat damaged neurons [34-36].

## Conclusion

Neurogeneration creates appropriate environment for glial cells to regenerate. But potential harmful effects have sidelined the studies for further development of nerve cells. Natural products such as hydrogen sulfide is important to control activation of microglia in CNS. Microglia has two effects, one it protects neurons and second transplantation of nerve cells. During injury microglia benefits neuronal stem cells. Since glial cells are the cellular components of environment surrounding neurons, their types play a major role in neural regeneration. Glial cells often create scar formation, but technology driven stem cells find various ways to convert these into neural cells. Glial scar often has its potential, they repair, inhibit and potentially regenerate CNS injured tissue. NG2 helps to proliferate, survive and differentiate stem cells in the brain, target the injured region and cure them. In conclusion appropriate control of glial cells can help in survival and efficient function of neural stem cells. These glial cells can be the future of treatment of CNS injuries and diseases. Since the discovery of iPSC, many disorders of CNS has been cured. It is clear that glial cells has contributed towards stem cell regeneration in CNS and are indispensable asset to brain homeostasis, disease cure, development and function of nerve cells. Along with fast paced progress of stem cells and cell replacement therapy, hiPSC derived glial cells will play crucial role on clinical treatment of neurological diseases.

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