Journal of Stem Cell Research

Genesis-JSCR-1(1)-04
Volume 1 | Issue 1
Open Access

Glial Cells Form an Integral Part of Nerve Cells Regeneration: Stem Cells End up Glia to Give Life to Nerve Damage

Prithiv K R Kumar[1*] and Albert Alukal[2]

[1]Director, Principle Scientist- Poichyadical Stem Cell Centre for Research and Development (POSCERD)Chicago, CEO- La'zer Health Care, Chicago, USA

[2]Chief Medical Officer- La'zer Healthcare, Chicago, USA

[*]**Corresponding author**: Prithiv K R Kumar, Director, Principle Scientist-Poichyadical Stem Cell Centre for Research and Development (POSCERD) Chicago, CEO- Lazer Health Care, Chicago, USA

Citation: Kumar PKR, Alukal A. (2020) Glial Cells Form an Integral Part of Nerve Cells Regeneration: Stem Cells End up Glia to Give Life to Nerve Damage. J Stem Cell Res. 1(1):1-14.

Received: June 06, 2020 | **Published:** June 25, 2020

Abstract

Glia is defined as non neuronal cells with support functions, also known for supporting neurons and maintaining stability and overall infrastructure of nervous system. Reflection of such roles forms adequate base for allocation of certain subtypes. First type is astrocytes which is star shaped, containing ion and highly branched microglia for performance of phagocytes and defence. Two other cells such as oligodendrocytes and Schwann cells both in Central Nervous System (CNS), and peripheral nervous system form the myelin sheet. And the latest addition to the club is the NG2-glia dispersed through CNS parenchyma.

Keywords

Glial cells: Neural stem cells: Nerve cells

Introduction

Neurons are considered the maps of brain. Their ability to communicate and generate actions in brain is regarded best for stabilisation. Glial cells often end up cleaning by removing excessive ions [1]. Even the transmitters are cleansed by astrocytes. In Central nervous system (CNS) and peripheral nervous system (PNS) Schwann cells are tasked to do that. But there is a different perspective in approach of glial cells. They serve in communication of synapsis, which contains two neuronal elements to send and receive synapsis. Another glia called NG2- glia which helps in forming the Perineuronal nets (PNN). These PNNs form extracellular DNA matrix which stabilizes the synapsis. An overall Schwann cell protects the entire synapse. Since the synapses are closed knit process and play important in communication and remodeling nerves, their number usually increases in brain with higher complexity [1] (Figure 1).

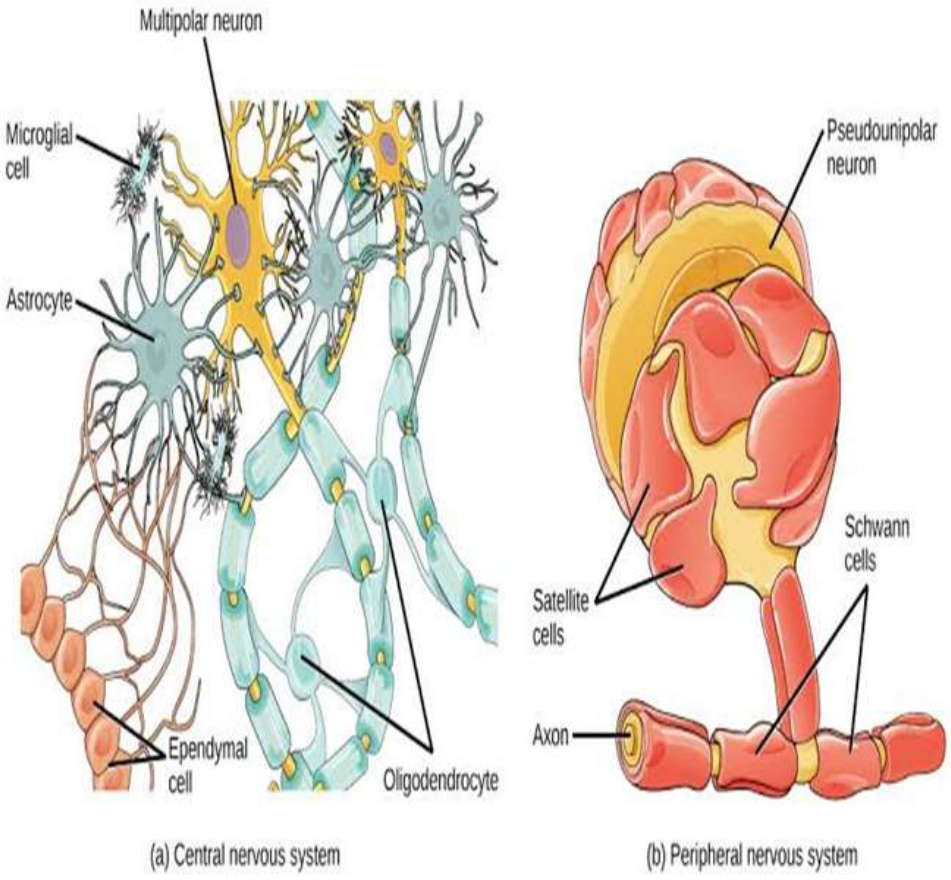

Figure 1: Shows the glial cells in CNS and PNS [1].

At a point of neuronal axis, glia and neurons have crossed each other. This particular moment specific glial cells and NG2 undergoes synaptic process and directs axons to various brain region including corpus callosum. Glial cells further intimidate oligodendrocyte progenitor cells to regenerate and proliferate in corpus callosum. Many NG2 are found in order to balance synaptic communication and progenitor cells

division [2]. As this process continues, several questions arise about synaptic communication, astrocytes performing stem cells function after injury. In this review these questions can be addressed. A stage will be set for central issues of glial functions, providing new insights to scar formation after injury and how glial cells plays a role in heterogeneity and nerve formation [2] (Figure 2).

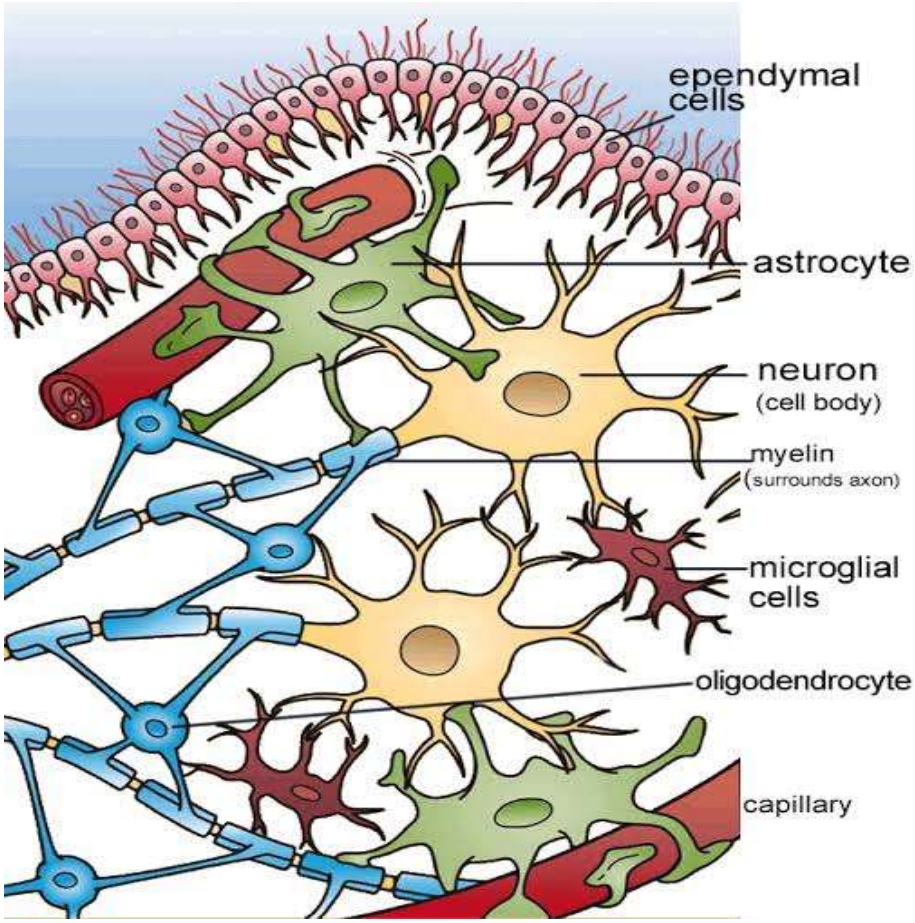

Figure 2: Shows neuroglia [1].

Glial Cells Origin and its Types

First glia to appear is radical glia or radical glial cells. They are seen all over brain. Radical glia develops neuro epithelial cells responsible for the formation of neural cells and neural tubes [3].

The differentiation of radial glial cells from neuroepithelial cells, acquires protein expression, transporters, synthase and granules. The expression namely vimentin, glial fibrillary acidic protein, transporter is astrocyte specific or GLAST, glutamine synthase and glycogen granules and filaments [4] (Figure 3). With the help of above combined process tools, radial glial cells expand several millimetres inside the cerebral cortex. It happens when brain thickens during development. The growth helps in stability or rather acts as function of support for radial glial cells and guidance to migrant neurons. This is an important role because migrant neurons may get disordered or mutated affecting them to causing neuronal dysplasia [5]. Enhancing the further research, glial have three types of cells. They are named

astrocytes, oligodendrocytes and microglia. Differing in origin, even markers and physiological functions and subtypes have allotted place in each type [6].

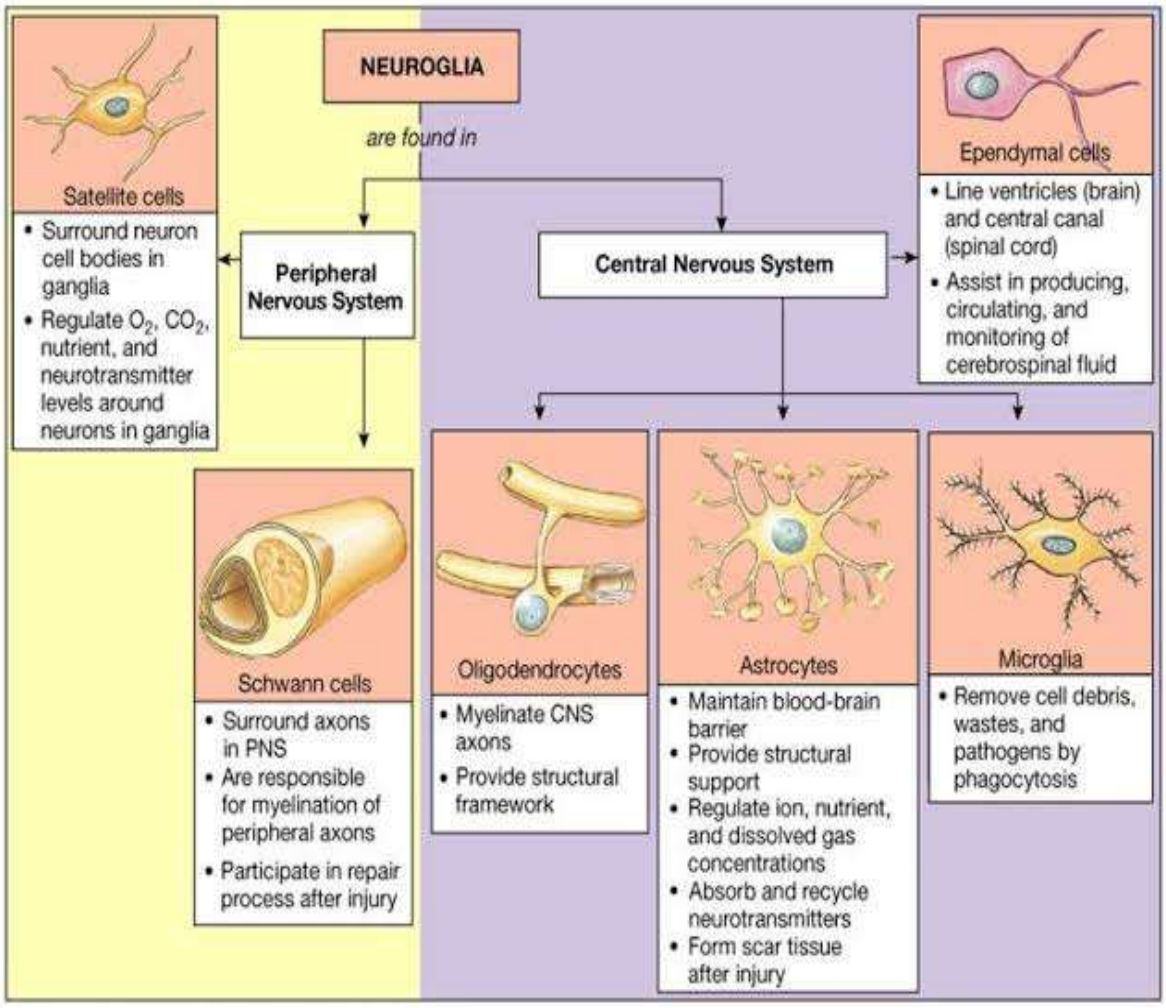

Figure 3: Shows the types of glial cells in both CNS and PNS [4].

Types of glial cells and their functions

Astrocytes play crucial role in function and development of brain. They are seen to differ in morphology, gene expression, metabolism and pathology. They are stellate cells found in both grey matter and white matter. Astrocytes net in receptors and transporters with K^+ channel and aquaporin channel receptor. These channels balance the osmotic levels and maintain potassium levels [6]. Transporters in astrocytes include glucose molecules and glutamate structures. Transporters are linked with gap junctions which contain calcium that release neurotransmitters such as ATP and serine. Hence they are termed glio transmitters; contain the ability to regulate the synaptic inputs of neurons. Astrocytes maintain the regulators and transporters at a particular distance; hence any loss could compensate the nervous breakdown. Basically four subunits are very distinct in glial fibrillary acidic protein (GFAP) of astrocytes. They are the positive cells in the human brain. The four subunits are protoplasmic astrocytes in grey

matter, inter laminar astrocyte, polarised and fibrous in white matter. The function is to ensheath the blood vessels. Figure 4 shows astrocyte [7].

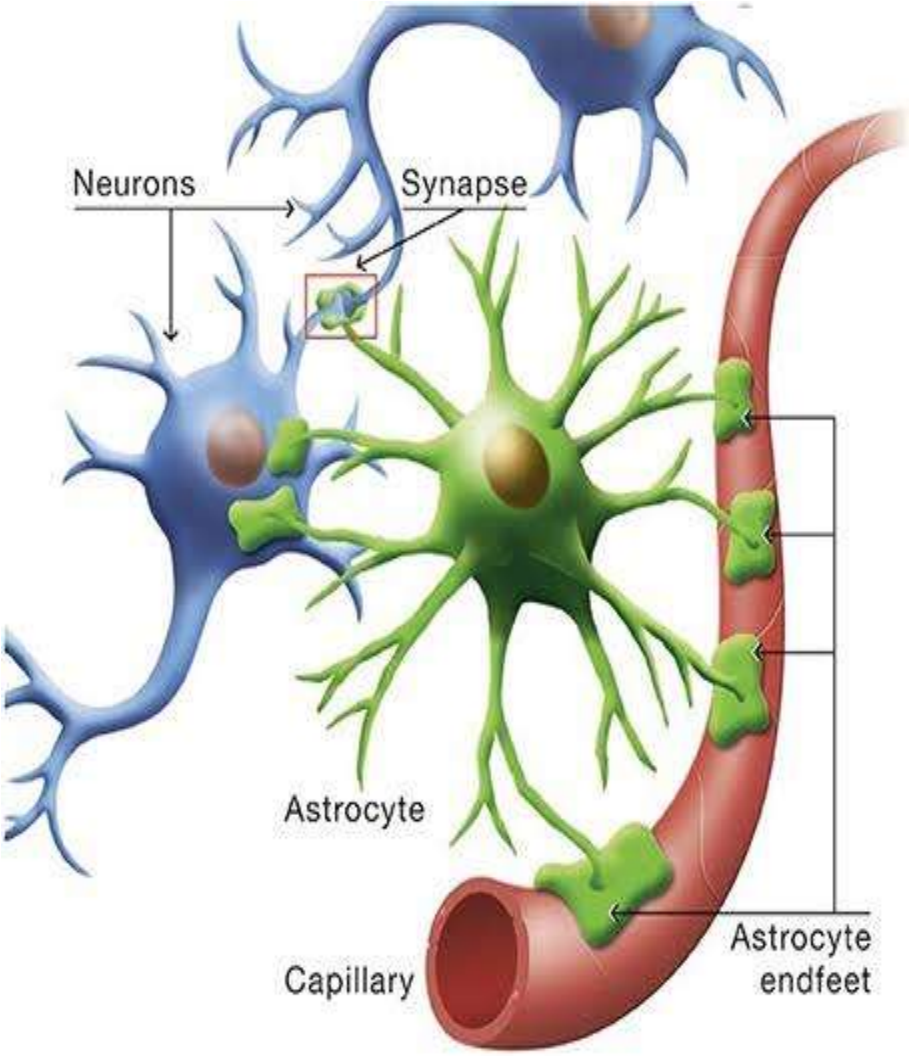

Figure 4: Shows astrocytes function [7].

Oligodendrocytes are found throughout CNS, and generated from OPCs [8]. They can differentiate in different cultures, and are present in white and grey matter with larger percentage in the latter. They are a mylineating cell that serves to maintain nerve condition and calibre and also promote axon survival. They regulate local neuronal environmentand represent mutual relationship between neuro and glia environment. OLs generally help in structural and neurotrophic support for neurons and neurons in return provide maturation to oligodendrocytes [8] (Figure 5).

Figure 5: Shows OL [8].

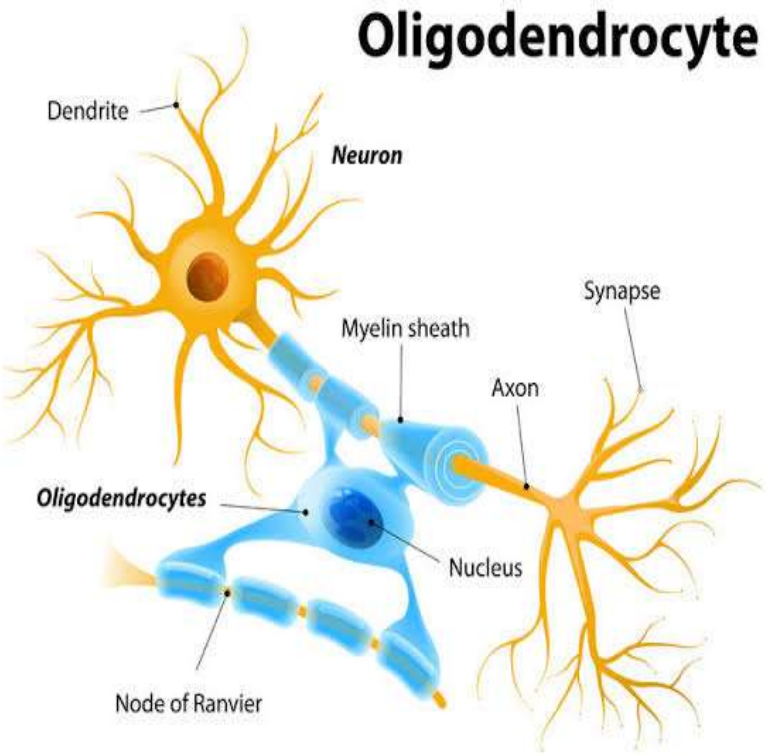

Figure 5: Shows OL [8].

Microglia forms the immune system in the brain and is the resident macrophage in the brain and spinal cord. The phagocyte debris, inflammation, pathogens and injury [9]; they form the frontline defence of CNS immune system. Microglia help in repairing damage tissue by activating themselves from dormant state depending on the signals and modulators. This is termed as polarisation. The activation range from pro-inflammatory M1 phenotypes to anti-inflammatory M2 with the bond of interferon. M2 is activated using interleukin IL3 type and IL 10 type transforming growth factor(TGF)[10] M1 microglia is pathogen responding cell types releasing pro-inflammation factors such as IL-6, IL-12, Tumour Necrosis Factor (TNF) and chemokine motif ligand (CCL) end up causing neurotoxicity. On the contrary M2 act as antagonising cells by releasing IL-10 and TGF for promotion of immune suppression and neuronal protection [9] (Figure 6,7).

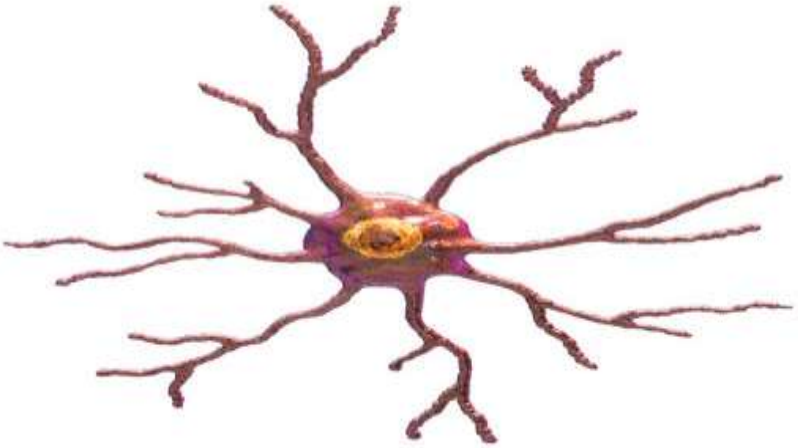

Figure 6: Shows microglia [10].

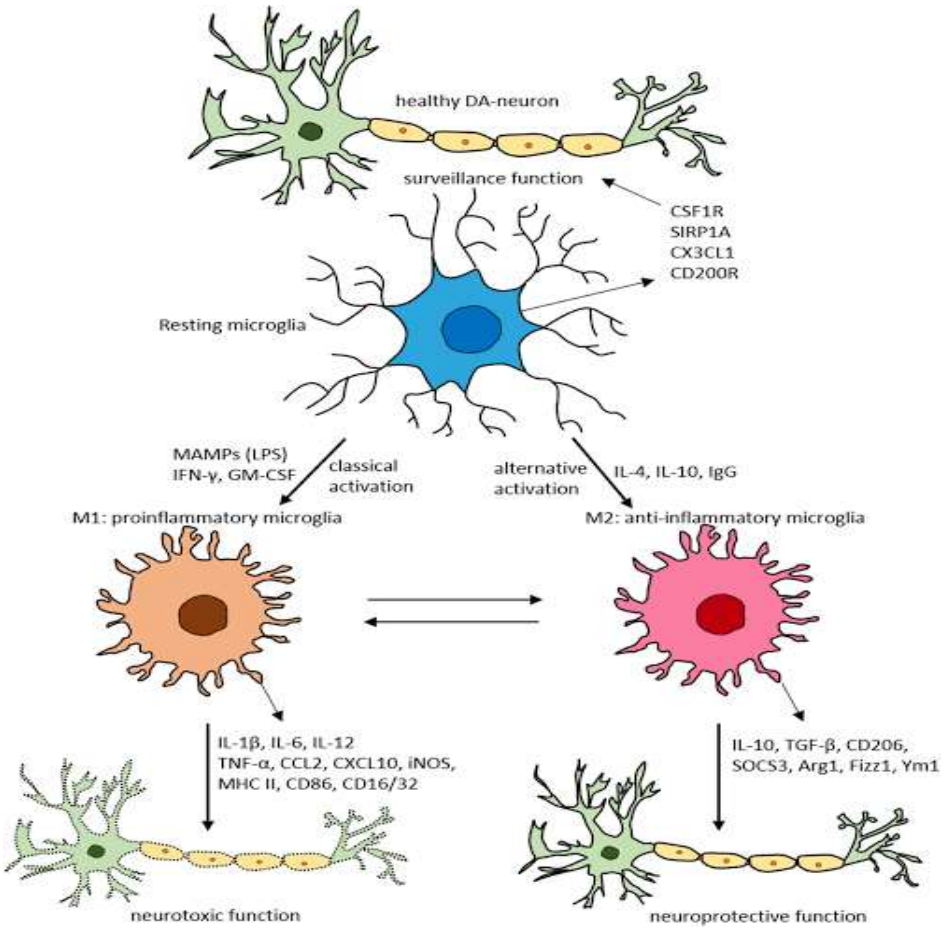

Figure 7: Shows microglia passive to active state [11].

Nerve glial Antigen 2 cells (NG2) form precursors to mature oligodendrocyte precursor cells (OPC) marker and growth factor receptor. They are expressed in macrophages and vascular mural pericytes. Other than expressing progenitor cells, they also express ion channel and conduct electric currents to self propogate and differentiate in OLs [11,12] (Figure 8).

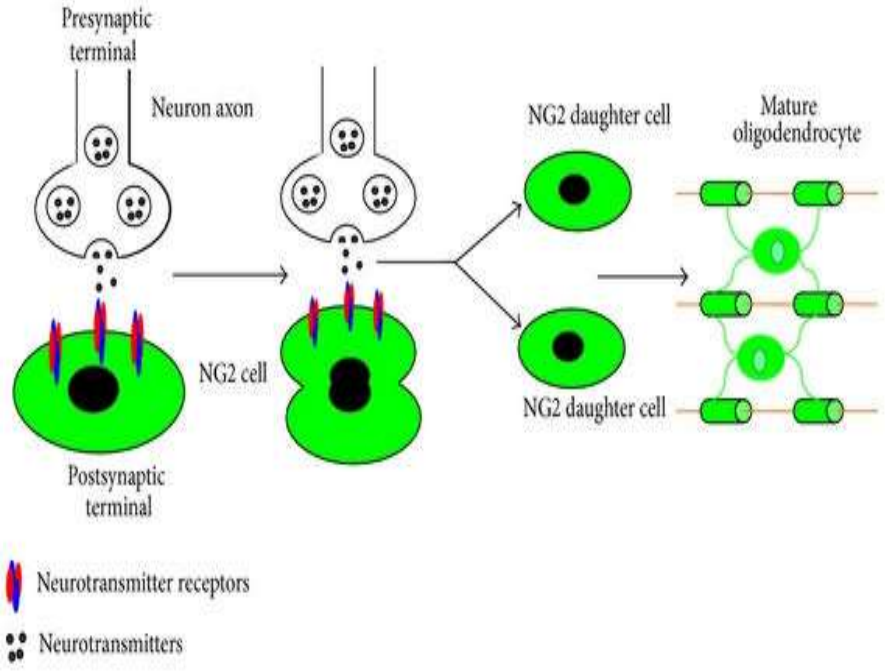

Figure 8: Shows NG2 cells [12].

The Term Called Gliogenesis

The process of glial occurring during neurogenesis. Radical glial cells generate new neurons and progenitors produce glial cells. They then switch to gliogenesis to produce astrocytes after being exposed to interleukins receptors [13]. Gliogenesis takes place in spinal cord with the start of motor neuronin the ventricular region. During this process basic helix to helix , helix to loop to helix transcription factor occurs which is the general expression of oligodendrocyte transcription factor[14]. The second wave of gliogenesis is formed in dorsal neural tube, Fibroblast Growth Factor (FGF), signalling Nkx6 protein. Third wave of gliogenesis occur at the birth of OPC. They are similar to production of OPC in spinal cords. The precursors are in the medial ganglionic area, showing eminence in the anterior entopeduncular area, slowly migrating to telenceplon and cortex. In this process they express a marker from platelet derived growth factor receptor alpha (PDGFRalpha). Final OPC production is from cortex under transcriptional control of Emx1 [14] (Figure 9).

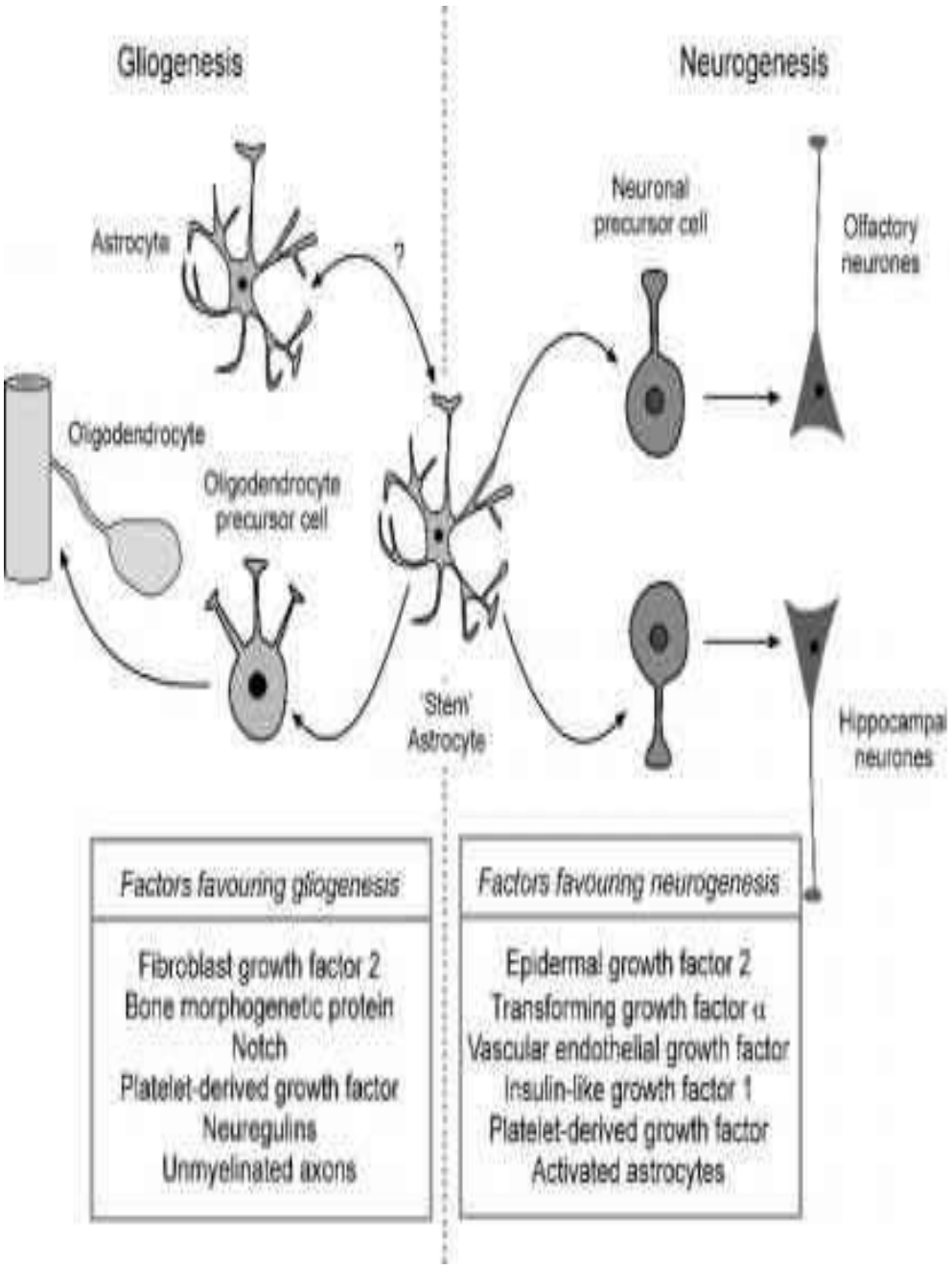

Figure 9: Shows gliogenesis and neurogenesis process [14].

Rudolf Virchow introduced neuroglia in 1850s, following that many neuro anatomists have contributed towards glial cells their functions and characteristics. Several discoveries from mechanical support of nervous tissue to metabolic functions and removal of toxics have all played important role in shaping glia. The peripheral glia which is called Schwann cells was named by Louis Antoine Ranvier in 1871 where node of Ranvier was named after. Theodor Schwann discovered the Schwann cells as myelin sheets in 1839. Astrocytes were defined as stellate glia cells by Michael Von Lenhossek in 1895. Later in in 1919 Del Rio Hortega attributed with identification of microglia and oligodendroglia. William Ford earlier had a sketch of oligodendrocyte, but Ng2 glia were not discovered until late 1980 by William

Stallup [15-17].

In 1950 Willaim Hildand colleagues made electrophysiological recordings of both vertebrates and invertebrates defining glia cells as electrically non excitable cells. For decades these discoveries were never challenged. Later these astrocytes were shown to generate calcium and potassium uptake, now becoming potential job of astrocytes in CNS. Leif Hertz proposed this idea in 1965. In 1980 Milton bright onduring electron microscopy study identified the gap functions in astrocytes [16]. Helmutt Kettenmann introduced GABA receptors and $ca2^{+}$ signals in mechanical and neurochemical stimulation. This led to discovery of astroglial intercellular $Ca2^{+}$ waves by Ann CornallBell. All these discoveries led to tripartite synapse, where astoglial is involved in neuronal synaptic transmission [17].

Myelinating Function

In 1884 discovery of myelin by William Norton put the end to suspicious nature of lipid layers. The lamellar structure of myelin with protein content was discovered by Fernandez-Moren and Shostrand. Norton revealed during myelin discovery, it contains 75-80% lipids and 15-30% protein depending on the source [18]. Microglia was largely not discovered till late 60s. Geor and his colleagues developed facial lesion experiments to discover microglial activities [15].

Regenerating Glial Cells to Repair Brain

Astrocyte regeneration

Astrocytes form neural stem cells in CNS. In adult brain they form self renewing clonal precursors for multi potent neurospheres. Also they can differentiate into neurons in the absence of exogenous growth factors. In the Cortical region of CNS these astrocytes form glial scar not neurons. In lesion site, astrocytes play crucial role in healing process. Microglia that migrates helps the astrocytes to repair tissue and form membrane protein. In order to undergo this process astrocytes have to proliferate and wound the areas of scar to form glial scar and reduce the spread of inflammation. Glial scar although serve to repair BBB(blood brain barrier), they also prevent overwhelming inflammatory response. Hence neuronal loss is reduced along with demyelination. Therefore glial scar treatment are useful for regeneration.Where experimentation is conducted treatment with peptide amphiphile helps in reducing glial scar formation and increase in number of oligodendroglia to protect the spinal cord injury [19-21].

Interleukins IFN beta encoding cells transports NSC (Neural Stem Cells) to glial cells in spinal cord to stimulate TLR4 signalling. Some discoveries have shown glial scars to help in wound healing and reduce inflammation and secure healthy tissues. However, the direct harvesting if glial scar has harmful effects. Introducing astrocytes to glial scar towards functional neurons becomes ideal for CNS regeneration. Astrocytes can be drawn towards neurons by forced expression of Pax6 transcription factor neurogenin-2, tbey are then isolated from cortex regenerated in vitro with pCAG neuro vector giving rise to synapse formation of glutamatergic neurons [20]. Astrocytes should be reprogrammed with separate transcription factors such as OCT4, NANOG, SOX2 which gives rise to neural stem cells. These astrocytes existing NSCs generate mature neurons containing expressions of synaptic proteins and transmitters.

There always existed problem in regeneration. This impasse was solved by Guo and his colleagues by reprogramming the functional neurons in adult mouse cortex during infection with single transcripted retrovirus factor namely NeuroD1. Astrocytes and NG2 cells are regenerated into glutamatergic neurons and GAB [21].

Microglia regeneration

Macrophages reside the microglia and help them migrate to lesion site producing inflammatory mediators such as IL-1, IL-6, TNF alpha, ROS and nitric oxide. They recruit leukocytes and act as local cells to surpass BBB by interacting local cells with BBB endothelial cells and astrocytes. This combination eliminates pathogens and clean up debris caused due to inflammation. The junction where microglia and neural stem cells meet plays a crucial role in regeneration of neurons. They activate the microglia to trigger chemical mediators such as neurontrophic factors to repair NSC and help in survival and differentiation of microglia as well as give essence to neurogenesis [22]. The activation of chronic microglial regeneration that destroys neural formation is controlled by caspase signalling. The chemical inhibition in these signalling stops microglial activation reducing neurotoxicity. Minocyline, an antibiotic known to enter BBB pathway inhibits the microglia and reduces exotoxins leading to neural death. In-vitro experiments on rat models, Minocyline show positive effects on endogenous neural stem cells survival. They also showed enhance protection of neurons in ischemic stroke in rats. Hydrogen sulfide has always proven effected in neuro protection. Hydrogen sulphide is used when Minocyline fails. Generally in traumatic CNS injuries, microglia activates and provides immune and self repairs. Franzen et al in 1998 macrophages contributes towards axonal regeneration in animal model using microglia. Microglia usually induces stem cell proliferation method to promote oligodendrocytes regeneration. Generation of neurons from white matter in brain is activated by microglia using trypsinogen PRSS2. Microglia then interacts with ES derived stem cells to recover CNS injury [21-23].

OL regeneration

Oligodendrocytes have less inflammatory response after CNS injury, due to high metabolic activity, intracellular ion and low antioxidants such as glutathione. OLs are usually triggered by proteolytic enzymes, chemical mediators and oxidative stress. Remyelination process is important to activate oligodendrocyte progenitor cells. NG2 gives rise to most OLs in CNS producing astrocytes and neurons [23]. NG2 proliferates, migrates to lesion site giving rise to oligodendrocytes to remyelinate neurons. NG2 glia act as adhesive substrate for axon growth and regenerates in front these axons after spinal cord injury. Since NG2 has limited growth, cytokine and inhibition factor for leukemia helps in differentiation and survival of OLs. In experimental studies it is shown that inhibition factors for leukemia reduces loss of OLs. Inhibition expands adult neural stem cells for self renewal, thus preventing the emergence of differentiated progeny. They show proliferation, survival, differentiation in cultivated ES cells giving rise to remyelination and neurogenesis [24] (Figure 10).

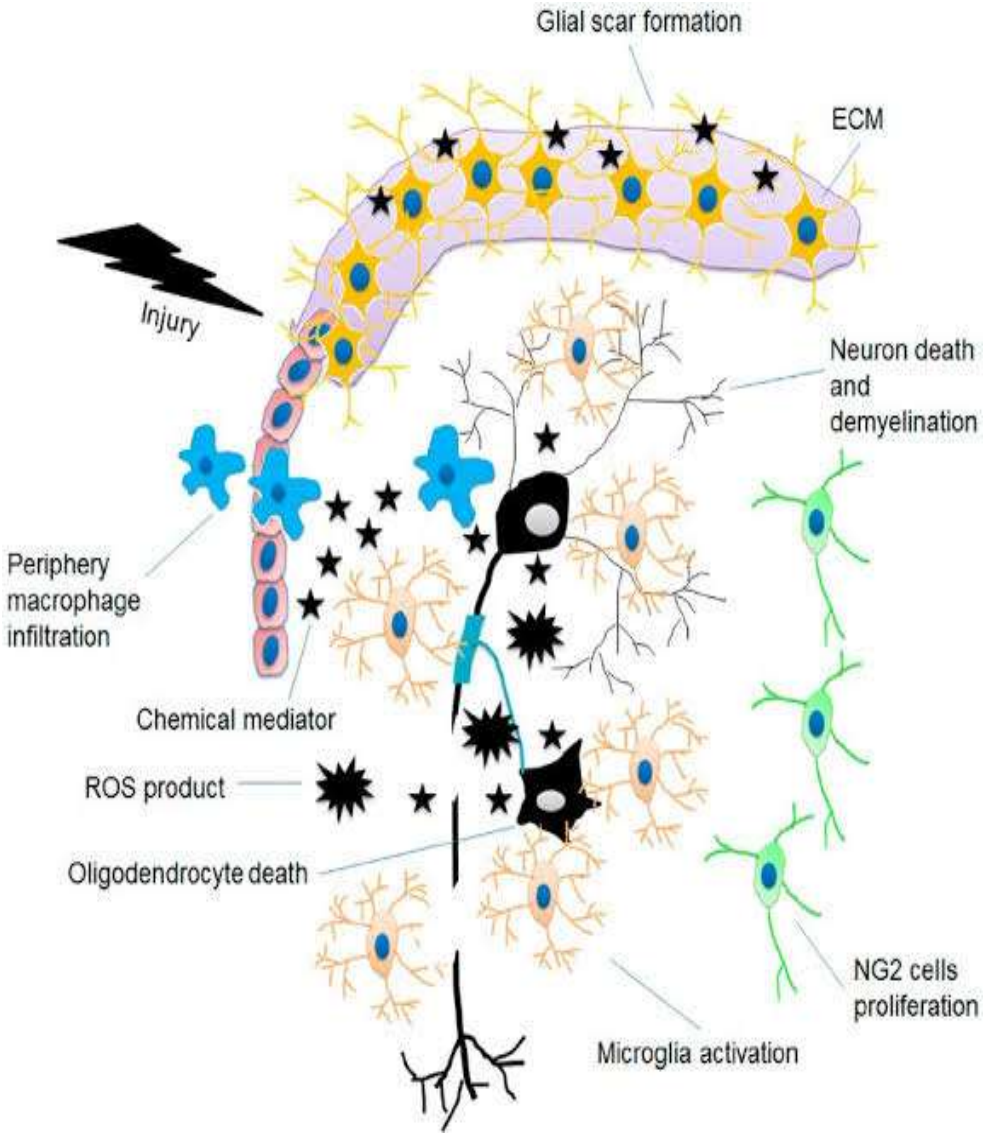

Figure 10: Shows glial cells regeneration after CNS injury [24].

Radial Glial Cells an Epithelial Hallmark

Radial glial cells highlight various proteins such as GFAP,GALST, GLT-1, Sox2, Hes5, Prominin1helping in self renewal and genetic fate mapping of neurogenesis over several months. Direct ventricular contact of cerebrospinal fluid during development, helps these radial glial cells to act as cellular signalling components. Proteins located in sub granular levels especially Promenin-1sorts apical membrane domain in neuroepithelial and radial glial cells spread along entire domain membrane of DG NSCs. Prominin-1 and GFAP expression targets highlights molecular similarity in the radial glial cells during development. With the help of radial morphology, the parenchymal astrocyte act as adult NSCs which self renew and give rise to intermediate progenitors then regenerate neuroblasts. Radial astrocytes shows prominence in Muller glia and Bergmann glia with similarities of radial glial cells morphology found in retina and cerebellum [25].

Only 10% of brain expresses NG2 and alpha transcriptase factor namely Olig2 and Sox10. NG2 division is a slow process in forebrain and might end up weeks to proliferate. Interestingly in post natal brain these glia is a fast process, depending on the cell cycle and regulation by signalling. Upon injury they regenerate in brain fast virtually proliferating cells outside niches of neurogenesis. NG2. PDGFRalpha and Olig2lines allow genetic recombination in adult brain. Surprisingly there are regions in which NG2 glia proliferates slower generating less mature oligodendrocytes depending in location [26]. An important factor of NG2 glia is itself renews and generates more progenitors for oligodendrocytes. They receive synapsis from neurons with specific specialisations such as GABA and glutamatergic also possessing transmitter receptors. Over a period of time NG2 glia can be changed by repeated stimulation of AMPA receptors on NG2 glia. Thus NG2 considered to have hallmark uniqueness for neurons and CNS [27]. While differentiating into oligodendrocytes NG2 losses synaptic input and myelination is no longer an option. It is necessary to show increases neuronal activity leading to generation if myelinating OLs. Through NG2 glia proliferation and regeneration in brain [28]. This function has caused the myelination to improve speed in information input and brain processing feature contributing to myelin remodelling. The discovery of NG2 glia has helped in recovery of brain after injury. These cells have the capacity to produce more than oligodendrocytes [28-30].

Conclusion

In conclusion, glial cells play a passive and supporting role in CNS. They have major contribution in brain homeostasis, development and functions and also participate in curing neurological diseases. Glial cells behaviour can improve the local microenvironment and survive differentiation of neuronal stem cells. They contribute towards future treatment of CNS injuries and diseases.

References

1. Corti S, Nizzardo M, Simone C, Falcone M, Donadoni C, et al. (2012) Direct reprogramming of human astrocytes into neural stem cells and neurons. Exp Cell Res. 318(13):1528-1541.
2. Cusulin C, Monni E, Ahlenius H, Wood J, Brune JC, et al. (2012) Embryonic stem cell-derived neural stem cells fuse with microglia and mature neurons. Stem Cells. 30(12):2657-2671.
3. Deierborg T, Roybon L, Inacio AR, Pesic J, Brundin P. (2010) Brain injury activates microglia that induce neural stem cell proliferation ex vivo and promote differentiation of neurosphere-derived cells into neurons and oligodendrocytes. Neuroscience. 171(4):1386-1396.
4. Dheen ST, Kaur C, Ling EA. (2007) Microglial activation and its implications in the brain diseases. Curr Med Chem. 14(11):1189-1197.
5. Dooley D, Vidal P, Hendrix S. (2014) Immunopharmacological intervention for successful neural stem cell therapy: New perspectives in CNS neurogenesis and repair. Pharmacol Ther. 141(1):21-31.
6. Cao X, Li LP, Wang Q, Wu Q, Hu HH, et al. (2013). Astrocyte-derived ATP modulates depressive-like behaviours. Nat Med. 19(6):773-777.
7. Chang A, Tourtellotte WW, Rudick R, Trapp BD. (2002) Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. N Engl J Med. 346(3):165-173.
8. Clarke LE, Barres BA. (2013) Emerging roles of astrocytes in neural circuit development. Nat Rev Neurosci. 14(5):311-321.

9. Colonna M, Butovsky O. (2017) Microglia functions in the central nervous system during health and neurodegeneration. Annu Rev Immunol. 35:441-468.
10. Crawford AH, Stockley JH, Tripathi RB, Richardson WD, Franklin RJ. (2014) Oligodendrocyte progenitors: adult stem cells of the central nervous system? Exp Neurol. 260:50-5.
11. Davies JE, Huang C, Proschel C, Noble M, Mayer-Proschel M, et al. (2006) Astrocytes derived from glial-restricted precursors promote spinal cord repair. J Biol. 5(3):7.
12. Douvaras P, Fossati V. (2015) Generation and isolation of oligodendrocyte progenitor cells from human pleuripotent stem cells. Nat Protoc. 10(8):1143-54.
13. Morgello S, Uson RR, Schwartz EJ, Haber RS. (1995) The human blood-brain barrier glucose transporter (GLUT1) is a glucose transporter of gray matter astrocytes. Glia. 14(1): 43-54.
14. Kumar PKR. (2020) Neural Stem cells: Several Methodology in Regenerative Medicine to Cure Brain Injury. Stem Cell Res. 1(1):1-13.
15. Baumann N, Pham-Dinh D (2001) Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiol Rev. 81(2):871-927.
16. Kang SH, Fukaya M, Yang JK, Rothstein JD, Bergles DE. (2010) $NG2^{+}$ CNS glial progenitors remain committed to the oligodendrocyte lineage in postnatal life and following neurodegeneration. Neuron. 68(4):668-681.
17. Zhu X, Bergles DE, Nishiyama A. (2008) NG2 cells generate both oligodendrocytes and gray matter astrocytes. Development. 135(1):145-157.
18. Nishiyama A, Polydendrocytes (2007) NG2 cells with many roles in development and repair of the CNS. Neuroscientist. 3(1):62-76.
19. Douvaras P, Fossati V. (2015) Generation and isolation of oligodendrocyte progenitor cells from human pluripotent stem cells. Nat Protoc. 10(8):1143.
20. Emdad L, D'Souza SL, Kothari HP, Qadeer ZA, Germano IM. (2012) Efficient differentiation of human embryonic and induced pluripotent stem cells into functional astrocytes. Stem Cells Dev. 21(3):404-10.
21. Fawcett JW, Asher RA. (1999). The glial scar and central nervous system repair. Brain Res. Bull. 49(6):377-91.
22. Ge WP, Miyawaki A, Gage FH, Jan YN, Jan LY. (2012) Local generation of glia is a major astrocyte source in postnatal cortex. Nature. 484(7394):376-80.
23. Goldman SA, Schanz S, Windrem MS (2008) Stem cell-based strategies for treating pediatric disorders of myelin. Hum Mol Genet. 17(R1):R76-83.
24. Kemp K, Mallam E, Scolding N, Wilkins A. (2010) Stem cells in genetic myelin disorders. Regen Med. 5(3):425-39.
25. Miller RH. (1996) Oligodendrocyte origins. Trends Neurosci. 19(5):159-61.
26. Svendsen CN, Smith AG. (1999) New prospects for human stem-cell therapy in the nervous system. Trends Neurosci. 22(8):357-64.
27. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. (2010) Mechanisms underlying inflammation in neurodegeneration. Cell. 140(6):918-34.
28. Goldman SA, Kuypers NJ (2015) How to make an oligodendrocyte. Development. 142(23):3983-95.
29. Ghoshal A, Das S, Ghosh S, Mishra MK, Sharma V, et al. (2007) Proinflammatory mediators released by activated microglia induces neuronal death in Japanese encephalitis. Glia. 55(5):483-96.
30. Kumar PKR, Alukal A. (2020) Stem Cells Cure for Brain Injury: A Novel Method to Cure Brain Trauma. Stem Cell Res. 1(1):1-10.