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·Review·

Roles of NG2 glial cells in diseases of the central nervous system

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Abstract: NG2 cells are a novel distinct class of central nervous system (CNS) glial cells, characterized by the expression of the chondroitin sulfate proteoglycan NG2. They have been detected in a variety of human CNS diseases. As morphological, physiological and biomolecular studies of NG2 cells have been conducted, their roles have been gradually revealed. Research on cellular and molecular mechanisms in the pathophysiological state was built on the preliminary findings of their physiological functions; and in turn, this helps to clarify their physiological roles and leads to the identification of novel therapeutic targets. This review summarizes recent findings regarding the potential roles of NG2 cells in traumatic brain injury, multiple sclerosis, glioma, epilepsy, Alzheimer's disease and electroconvulsive therapy for depression.

Keywords: NG2 cell; electrophysiology; multiple sclerosis; glioma; Alzheimer's disease; epilepsy

1 Introduction

NG2 cells are a distinct class of glial cells in the central nervous system (CNS). Their discovery revealed the existence of a fifth major cell population in the CNS, the other four being neurons, mature oligodendrocytes, astrocytes and microglia. This finding also indicated that the mature CNS contains an abundant supply of precursor cells, which are widely distributed. Nowadays, research on NG2 cells is going through a second phase, aided by advanced methods and technologies[1]. Recent experimental results demonstrate that NG2 cells play critical roles in a variety of human CNS diseases.

2 Physiological characteristics of NG2 cells

Most NG2 cells arise from the medial ganglionic eminence and the anterior entopeduncular region, with a minor contribution from radial glia[2,3]. NG2 cells can differentiate into oligodendrocytes, thus they are also known as oligodendrocyte progenitor cells (OPCs)[4-10]. The *in vivo* fate of NG2 cells was examined in mice that were double transgenic for NG2creBAC (bacterial artificial chromosome) and the Cre reporter lacZ/EGFP. In the gray matter of these transgenic mice, they can differentiate into protoplasmic astrocytes, while in white matter they cannot[11]. Studies have shown that NG2 cells *in vitro* can give rise to neurons, but this is highly debated[12-19]. For an extensive description of the fate-choice mechanism, which is beyond the scope of this review, please refer to the original articles.

NG2 cells respond to glutamate in an alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor (AMPAR)-dependent manner. They do not exhibit currents or possess glutamate transporter 1 (GLT-1) or glutamate/aspartate transporter (GLAST) protein or mRNA[20]. Electrophysiological studies on mouse hippocampal slices

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and acutely isolated rat hippocampal glial cells using whole-cell patch clamp revealed that NG2 cells have a relatively high input resistance and express outward rectifying potassium currents with little inward current[21]. The structure of the neuron-glia synapses found on NG2 cells differs from that of neuron-neuron synapses by having a less well-defined postsynaptic density and smaller presynaptic boutons that contain fewer vesicles[22]. Fast neuron-glia synaptic transmission has been found between hippocampal neurons and NG2 cells. Glutamatergic signaling influences intracellular calcium levels in NG2 cells by activating calcium-permeable AMPA receptors, and these inputs are potentiated by high-frequency stimulation[23].

3 NG2 cells in diseased CNS

3.1 NG2 cells as a double-edged sword in brain injury Traumas, such as needle puncture and knife damage, induce an increase in progenitor proliferation and a coincident increase in NG2 proteoglycan expression under acute post-injury (PI) conditions, which are known to persist for 14–21 days[24]. Progenitor proliferation decreases on the transition from the acute to the chronic PI phase[25]. In conjunction, viral studies suggest that NG2 proteoglycan transcription levels decline. Despite the reduced mRNA (to basal level), NG2 proteoglycan levels persist and become inherited by the offspring cells derived from progenitors. Tissue repair continues after injury and begins with the formation of a gliotic scar. Similar findings are also reported in focal cerebral ischemia models. The NG2 proteoglycan appears as two subtypes: one at 290 kDa occurring in intact brain, and the other at 300 kDa in regions of necrotic injury. The larger cell bodies and thicker processes in the ischemic sites result from NG2 cell proliferation. They prevent the spread of damage to normal tissues, and some gradually differentiate into oligodendrocytes and contribute to remyelination[26-29].

However, they do have a negative impact as well. During the chronic PI phase, excessive accumulation of NG2 proteoglycan interferes with neurite growth *in vitro* and even prevents the newly sprouting axons from regenerating past the gliotic barrier and into the injury site. In addition, the cellular deficit incurred by the injury can bias the fate selection and contribute to a predominantly injurious phenotype. Therefore, progenitors in the context of injury may have a homogenous phenotype, less diverse than that in the intact CNS[24].

3.2 Remyelination in multiple sclerosis (MS): NG2 cells function as OPCs The relative number of NG2 cells varies in different types of MS lesion in different reports[30-36]. However, the conclusion can be drawn that NG2 cells are responsible for rapid and efficient myelin repair. Acute demyelination is repaired efficiently, while remyelination fails in chronic lesions[37]. This may result from an insufficiency or the depletion of NG2 cells over time, since quantitative analysis shows that NG2 cells only account for less than 5% of the total number of glial cells, while the number of oligodendrocytes is approximately 10-fold higher[38].

The discovery of autoantibodies to NG2 proteoglycan in the cerebrospinal fluid of MS patients is particularly important. They not only disrupt the remyelination process by destroying NG2-positive OPCs and blocking their migration, but also interact with the nodes of Ranvier to interfere with signal transduction[39]. These endogenous NG2 antibodies are considered to be the main cause of MS.

On the one hand, lovastatin (HMG-CoA reductase inhibitor)[40], glamorgan acetate[41], guanosine or guanine[42], ciliary neurotrophic factor[43], thymosin β4[44], and endogenous leukemia inhibitory factor[45], through different cascades of signal transduction, increase the numbers of NG2 cells and oligodendrocytes, and put an end to the demyelination process. The expression of platelet-derived growth factor α receptors (PDGFαRs) increases during the proliferation of NG2 cells, and NG2 proteoglycan expression disappears as NG2 cells differentiate into mature oligodendrocytes[46]. However, it is not the intention of this article to present a detailed review of the signaling pathways in MS.

On the other hand, chemokine stromal cell-derived factor-1, known as a developmental molecule to direct the

migration, proliferation, and differentiation of neuronal precursor cells within the developing CNS, is significantly up-regulated within activated astrocytes and microglia during demyelination, as are chemokine stromal cell-derived factor receptor 4 (CXCR4)-positive NG2 cells, or OPCs. Loss of CXCR4 signaling via either pharmacological blockade or *in vivo* RNA silencing leads to decreased OPC maturation and failure of remyelination. Therefore, CXCR4 activation, by promoting the differentiation of OPCs into oligodendrocytes, is critical for remyelination in the injured adult CNS[47].

3.3 Critical roles of NG2 cells and NG2 proteoglycan in glioma Many human gliomas carry markers of OPCs, such as NG2 proteoglycan, PDGFαR and Olig-2, suggesting that these progenitors are the original cells for glioma initiation[48-50]. The sensitivity of these progenitors to mitogenic stimulation may play a role in their susceptibility to transformation. Indeed, transformation via overexpression of PDGF provides the basis for a number of commonly-used rodent glioma models[51-54]. Molecular interactions allow NG2 proteoglycan to contribute to critical processes such as cell proliferation, glioma vasculature, cell motility and cell survival. Moreover, several reports have correlated the expression of NG2 proteoglycan with the degree of malignancy of the glioma[55-60].

3.3.1 On glioma cell motility NG2 proteoglycan, the extended central D2 domain of which binds to type VI collagen, acts as a linkage between the cell surface and the extracellular matrix[61,62]. Similar results have been achieved on laminin 2-coated surfaces[63,64]. The roles of collagen VI and laminin 2 in brain vasculature and their association with axonal processes provide a means for migration of NG2-positive glioma cells along blood vessels and nerve fiber tracts[65].

NG2 may be an important linker between endothelial cells and pericytes. Vascular endothelial cells do not express NG2 proteoglycan, but exposure to NG2 stimulates the motility of glioma cells. This *trans* effect is due to the interaction of the proteoglycan with the galectin-3/α3β1 integrin complex on the endothelial cell surface, resulting in enhanced β1 integrin signaling, greater endothelial cell motility and enhanced endothelial tube formation *in vitro*, and dramatically increased blood vessel development *in vivo*[66].

NG2 has been implicated as a co-receptor for β1 integrin ligands. In addition, NG2 and α3β1 integrin are co-expressed and form a physical complex on the cell surface. Upon stimulation by phorbol-12-myristate-13-acetate (PMA) or PDGF, the motility of NG2-positive cells increases significantly compared to that of NG2-null cells[67,68]. Further investigation has shown that both PMA and PDGF trigger protein kinase C α (PKCα)-dependent phosphorylation of NG2 proteoglycan at Thr2256, and that this phosphorylation event is required for the increase of motility. Moreover, phosphorylated NG2 at Thr2256 is co-localized with α3β1 integrin in broad lamellipodia at the leading edges of motile cells. NG2 phosphorylation at Thr2256 is responsible for relocation of the NG2/integrin complex to lamellipodia, accompanied by increased cell motility[69,70].

3.3.2 On glioma cell proliferation NG2 proteoglycan binds to fibroblast growth factor 2 (FGF2) and PDGF-AA with high affinity[71]. The core protein of NG2, rather than the chondroitin sulfate chain, serves as a co-receptor for FGF family members, with putative binding sites scattered throughout the D2 and D3 domains[72]. Both FGF2 and PDGF-AA are critical for expansion of the oligodendrocyte progenitor population.

In addition, phosphorylation of NG2 plays a role in cell proliferation. Extracellular signal-regulated kinase catalyzes the phosphorylation of NG2 at Thr2314, stimulating cell proliferation. Interestingly, α3β1 integrin activation is also required for this NG2-dependent increase in proliferation. NG2 phosphorylated at Thr2314 is co-localized with α3β1 integrin on microprojections on the apical cell surface. The integrin interacts with a set of signaling molecules, different from those needed in the motility mechanism[73].

3.3.3 On glioma cell survival Chemoresistance is an important problem occurring in the drug treatment of many gliomas. Intriguingly, apart from its effects on cell proliferation and migration, NG2-dependent activation of α3β1 integrin also has effects on cell survival due to increased

signaling through the phosphatidylinositol 3-kinase (PI3K) pathway[74]. In all cases, the NG2 expression level has direct correlations with both β1 integrin activation and the level of PI3K phosphorylation[75].

3.4 Fate-choice change of NG2 cells in some CNS diseases

3.4.1 Alzheimer's disease (AD) *In vitro* experiments suggest that neuronal induction is inhibited by elevated levels of amyloid β peptide (Aβ, a hallmark of AD pathology) in AD progenitor cells and in Aβ-treated healthy control progenitor cells, through a mechanism of β-catenin signaling interference which results in decreased expression of proneural genes. Moreover, Aβ has been shown to activate glycogen synthase kinase 3 (GSK-3β, an enzyme that phosphorylates β-catenin)[76], leading to the degradation of β-catenin and inactivation of the Wnt signaling pathway[77]. The activation of Wnt signaling can reverse Aβ fibril-induced neurodegeneration and behavioral impairment[78,79], while inhibition of the Wnt/β-catenin pathway prevents the differentiation of NG2 cells and other precursor cells[80,81]. The formation of the β-catenin/T-cell factor (TCF)/lymphoid enhancer factor-1 (LEF-1) complex is critical to the transcriptional regulation of target genes by the Wnt/β-catenin signaling pathway. LEF-1 and β-catenin form a ternary complex with DNA and change the DNA bend[82]. In the presence of Wnt/β-catenin signaling, β-catenin turns TCF into a transcriptional activator[83,84]. Even a transient toxic dose of Aβ can cause permanent damage to NG2 cells and other precursor cells by increasing the levels of GSK-3β, which in turn cause decreases of β-catenin levels leading to the down-regulation of proneural gene transcription and an impairment of neuron induction[85].

In conclusion, Aβ toxicity may diminish the multipotential capability of NG2 cells and other neural precursor cells by disrupting β-catenin signaling so that GSK-3β levels increase, causing the phosphorylation and degradation of β-catenin, which leads to reduced proneural gene expression. Therefore, although glial progenitor cells (GPCs) still exist in the brains of AD patients, they are unable to generate adequate numbers of new neurons to compensate for the neuronal loss caused by Aβ aggregation. If this mechanism really exists, reagents like PKC agonists or lovastatin (a reagent that may affect cholesterol synthesis and reduce Aβ production) can be used to defend against Aβ-induced neuronal damage[86,87]. The development of therapeutic approaches to inhibit GSK-3β and/or elevate β-catenin in NG2 cells or GPCs and other neural progenitor cells may help inhibit the toxic effects of Aβ and promote neurogenesis in AD patients[88].

3.4.2 Epilepsy Hippocampal neurogenesis declines substantially in chronic temporal lobe epilepsy (TLE). Studies have revealed that only 4%–5% of newborn cells differentiate into neurons in the chronically epileptic hippocampus, in comparison to 73%–80% in the intact hippocampus. Moreover, approximately 79% of newborn cells differentiate into astrocytes or NG2 cells in the chronically epileptic hippocampus, which is higher than the 25% in the intact hippocampus. Thus, severely diminished neurogenesis in chronic TLE does not correlate with decreased production of new cells or reduced survival of newborn cells in the subgranular zone-granule cell layer. Instead, it is associated with a dramatic decline in the neuronal fate-choice of newly generated cells. Overall, the newborn cells mainly differentiate into glial cells in chronic TLE, compared to the predominant neuronal fate in control conditions[89,90].

NG2 cells contain AMPA receptors rather than glutamate transporters; in contrast, astrocytes express glutamate transporters without AMPA receptors. Electrophysiological studies have revealed that rat hippocampal NG2 cells have a resting membrane potential more depolarized than that of astrocytes[20,21]. Impressively, several studies support the hypothesis that reduced or dysfunctional glial glutamate transporters in the hippocampus may trigger spontaneous seizures in patients with mesial temporal sclerosis[91], yet the underlying mechanisms are unclear. However, functional and single-cell transcript analyses support the idea that enhanced expression of glutamic acid receptor 1 is responsible for the prolonged receptor responses observed in the hippocampal astrocytes of epilepsy patients with mesial temporal sclerosis[92,93]. This alteration predicts enhanced depolarization upon activation by endogenous glutamate.

Prolonged receptor-opening promotes the influx of calcium and sodium ions, the latter of which block astroglial Kir channels[94], further strengthening depolarization. However, it remains unclear whether the changes in glial receptor function are the results of epilepsy. It is important that hippocampal NG2 cells lack gap junctional coupling but receive direct synaptic inputs from GABAergic and glutamatergic neurons[95,96], which may constitute an important mechanism in the generation of hyperexcitability. Thus it is critical to clarify the relative roles of astrocytes versus NG2 cells in epilepsy.

As NG2 cells may regulate excitability, it seems probable that they have a functional role in the hyperexcitability characteristic of epilepsy, although available data are inconsistent. The exact changes occurring in NG2 cell functioning during epilepsy still need further investigation.

3.4.3 Electroconvulsive therapy (ECT) and depression Volumetric changes and glial pathology have been reported in the CNS of patients with depression, an illness often associated with elevated glucocorticoid levels. Glucocorticoids reduce gliogenesis in the adult rat CNS. Loss of glial cells has been reported in depression and *de novo* formation of glial cells may thus have an important therapeutic role. ECT is a very efficient treatment for severe depression. Studies in animal models have found enhanced glial proliferation in response to electroconvulsive seizure (ECS) treatment, the counterpart of ECT for rats with elevated glucocorticoid levels[97]. In conclusion, ECS treatment induces transient glial cell activation in several brain areas, as detected by immunohistochemical analysis of the morphology and expression of markers typical of reactive microglia, NG2 cells and astrocytes[98].

ECS counteracts the glucocorticoid-induced inhibition of proliferation of NG2 cells, microcytes and oligodendrocytes, and the gliogenesis rate is restored to the baseline level[99]. This result adds to an increasing number of studies suggesting that antidepressant treatment counteracts the degenerative processes associated with major depression[100,101]. However, glial cell proliferation and activation also occur in response to neuronal damage, and cognitive side-effects have raised concerns as to whether ECT causes cellular damage in vulnerable brain regions and thereby leads to the activation of glia. Whether similar processes indeed play a role in the therapeutic effect of clinically administered ECT or contribute to its side-effects requires further investigation.

4 Conclusion

NG2 cells have long been recognized to play an essential role in a variety of human CNS diseases. However, the current data on their functional roles are still superficial. The intimate relationship of NG2 cells with axons and synapses renders them extremely sensitive to changes in the neuronal environment, allowing them to respond to pathological challenges by rapid proliferation, differentiation and migration. Moreover, NG2 proteoglycan interacts with growth factors and extracellular matrix, and activates the subsequent cascades of signal molecules. Thus it is considered not only as the marker of a specific cell type, but also as a marker of "activated" status (i.e. development, injury and pathology). More importantly, since NG2 cells can give rise to other cells, it is possible that disturbance in the lineage decision and plasticity of NG2 cells results in CNS diseases, especially AD and epilepsy. Overall, it is not surprising that NG2 cells in the adult CNS are a dynamic and heterogeneous population.

Subsequent studies have tried to identify the mechanisms by which NG2 influences various aspects of cell behavior including proliferation and migration. Functional understanding of the cellular and molecular alterations of NG2 cells in MS will help to clarify the physiological roles of NG2 cells in neural function. Further studies of NG2 cells in glioma may lead to the identification of novel molecular targets. It is also important to investigate the cellular and molecular properties of subsets of hippocampal glial cells in human epileptic tissue and to unravel the course of their functional alterations.

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NG2 细胞与中枢神经系统疾病

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摘要：NG2细胞是新发现的一类广泛存在于成熟和发育期中枢神经系统的胶质细胞群体。这些细胞表面表达NG2硫酸软骨素蛋白多糖，因而常被称作NG2细胞。随着NG2细胞形态学研究的深入，NG2胶质细胞的功能也越来越受到关注。NG2细胞在人类多种中枢神经系统疾病中扮演重要角色。本文结合最新的研究报道，就其在一些常见的中枢神经系统疾病中的作用进行概括综述。

关键词：NG2细胞；电生理学；多发性硬化；胶质瘤；阿尔茨海默病；癫痫