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Review

Reprogramming of astrocytes and glioma cells into neurons for central nervous system repair and glioblastoma therapy

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ABSTRACT

Central nervous system (CNS) damage is usually irreversible owing to the limited regenerative capability of neurons. Following CNS injury, astrocytes are reactively activated and are the key cells involved in post-injury repair mechanisms. Consequently, research on the reprogramming of reactive astrocytes into neurons could provide new directions for the restoration of neural function after CNS injury and in the promotion of recovery in various neurodegenerative diseases. This review aims to provide an overview of the means through which reactive astrocytes around lesions can be reprogrammed into neurons, to elucidate the intrinsic connection between the two cell types from a neurogenesis perspective, and to summarize what is known about the neurotranscription factors, small-molecule compounds and MicroRNA that play major roles in astrocyte

Abbreviations: AAV, adeno-associated virus; AD, Alzheimer's disease; ALC5, Activin-like receptor kinase 5; AP-1, activator protein 1; APC, adenomatous polyposis coli; Ascl1, achaete-scute family bHLH transcription factor 1; BFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BBB, blood-brain barrier; BEV, bevacizumab; BRD8, bromodomain containing 8; Brn2, POU class 3 homeobox 2; CAR, chimeric antigen receptor; CDKN2A, cyclin dependent kinase inhibitor 2A; CEND1, cell cycle exit and neuronal differentiation 1; CHAT, choline acetyltransferase; Chd7, Chromodomain helicase DNA-binding protein 7; CK1, Casein Kinase 1; NS, Central nervous system; CSPGs, chondroitin sulfate proteoglycans; CTIP2, COUP-TF interacting protein 2; Ctip2, chicken ovalbumin upstream promoter transcription factor-interacting protein 2; DAPT, 24-diamino-5-phenylthiazole; DCX, doublecortin; DLX2, distal-less homeobox 2; DNMT1, DNA methyltransferase 1; DLL1, delta-like 1; DRG, dorsal root ganglion; EphrinB3, ephrin B3; FOXG1, forkhead box G1; GABA, gamma-aminobutyric acid; GAD67, glutamate decarboxylase 67; GBM, glioblastoma; GFAP, glial fibrillary acidic protein; GSK3, glycogen synthase kinase 3; GSK3β, glycogen synthase kinase 3 beta; HESC, shuman embryonic stem cells; HMG, high mobility group; HiPSCs, human-induced pluripotent stem cells; Id1-3, inhibitor of DNA-binding 1–3; IL-1, interleukin one; IL-6, interleukin-6; INs, induced neurons; Insm1, insulinoma-associated protein 1; JAK, Janus kinase; JAK-STAT, Janus kinase signal transducer and activator of transcription; JNK, c-Jun N-terminal kinase; Klf10, Krüppel-like factor 10; LCMV, lymphocytic choriomeningitis virus; LIF, leukemia inhibitory factor; LMX1A, LIM homeobox transcription factor 1 alpha; MAGs, myelin-associated glycoproteins; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; MTOR, mechanistic target of rapamycin kinase; Myt1, Myelin Transcription Factor 1; NANOG, Nanog Homeobox; Myt1l, myelin transcription factor 1 like; NC, neuroblastoma cells; NF200, neurofilament 200; ICD, Notch intracellular domain; NKX6.1, NK6 homeobox 1; NPC, neural progenitor cell; NSC, neural stem cell; NSPC, neural stem/progenitor cell; NeuN, neuronal nuclear antigen; NeuroD1, Neurogenic differentiation 1; NeuroD4, neurogenic differentiation 4; Neurog2, neurogenin 2; NGN2, neurogenin-2; Nurr1, nuclear receptor related 1 protein; Oct4, octamer-binding transcription factor 4; OMgp, oligodendrocyte myelin glycoprotein; OPCs, Oligodendrocyte precursor cells; Par3, protease-activated receptor 3; Pax6, paired box protein 6; PCNA, proliferating cell nuclear antigen; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTBP1, Polypyrimidine tract-binding protein 1; PVALB, parvalbumin; RAC1, Ras-related C3 botulinum toxin substrate 1; RACs, Reactive astrocytes; REST, RE-1 silencing transcription factor; RG, radial glial; ROCK, Rho-associated protein kinase; R-Smad, receptor activated SMAD; SAG, Smoothened agonist; SEM4D, sema domain, immunoglobulin domain Ig, transmembrane domain TM and short cytoplasmic domain, semaphorin 4D); Smad, homolog of mothers against decapentaplegic; Sema3A, semaphorin 3A; Sema4D, semaphorin 4D; SGL, subgranular layer; SOX2, sex determining region Y-box 2; SOX11, Sex Determining Region Y-Box 11; STAT, signal transducer and activator of transcription; STAT3, signal transducer and activator of transcription 3; SV2, synaptic vesicle protein 2; SVZ, subventricular zone; SYN1, synapsin 1; TAAs, tumor-associated antigens; TCF, transcription factors; TGF-β, Transforming growth factor beta; TH, tyrosine hydroxylase; TMZ, temozolomide; TNF-α, tumor necrosis factor alpha; TUJ1, Taurine upregulated 1; VPA, Valproic acid; VGLUT1, vesicular glutamate transporter 1; VGLUT2, vesicular glutamate transporter 2; β-Trcp, bcta-transducin repeats-containing proteins.

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reprogramming. As the malignant proliferation of astrocytes promotes the development of glioblastoma multiforme (GBM), this review also examines the research advances on and the theoretical basis for the reprogramming of GBM cells into neurons and discusses the advantages of such approaches over traditional treatment modalities. This comprehensive review provides new insights into the field of GBM therapy and theoretical insights into the mechanisms of neurological recovery following neurological injury and in GBM treatment.

1. Introduction

During neurogenesis in the CNS, neural stem cells (NSCs) differentiate into neurons and glial cells (Fig. 1); moreover, neurons are terminally differentiated cells that gradually lose their regenerative capacity during development and maturation as a result of transcriptomic changes and chromatin remodeling processes [1]. Although astrocytes reactively proliferate, the capacity for neuronal regeneration is further impaired following CNS injury, during which the formation of a glial scar is promoted through communications with microglia, and large amounts of neurotransmitters are secreted, further impeding neuronal regeneration (Fig. 1). Therefore, the induction of neural recovery has become a primary therapeutic challenge following neuronal death caused by CNS injury. Stroke is the most common CNS injury disease [2]. Studies have found that inducing reprogramming of reactive astrocytes into neurons after stroke can help promote neurological recovery after injury [3]. However, except for stroke, neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, are also major causes of CNS damage. The lesions are mostly characterized by abnormal aggregation of proteins, triggering inflammatory reactions, neuronal damage and death, and destruction of neuronal networks, ultimately leading to neurometabolic dysfunction [4]. In this process, the abnormal proliferation of glial cells, including astrocytes, plays an important pathogenic role [5], and the reactive activation of astrocytes is a major pathological change in AD tissues, reactive astrocytes contribute to the neuroinflammatory changes in AD through the release

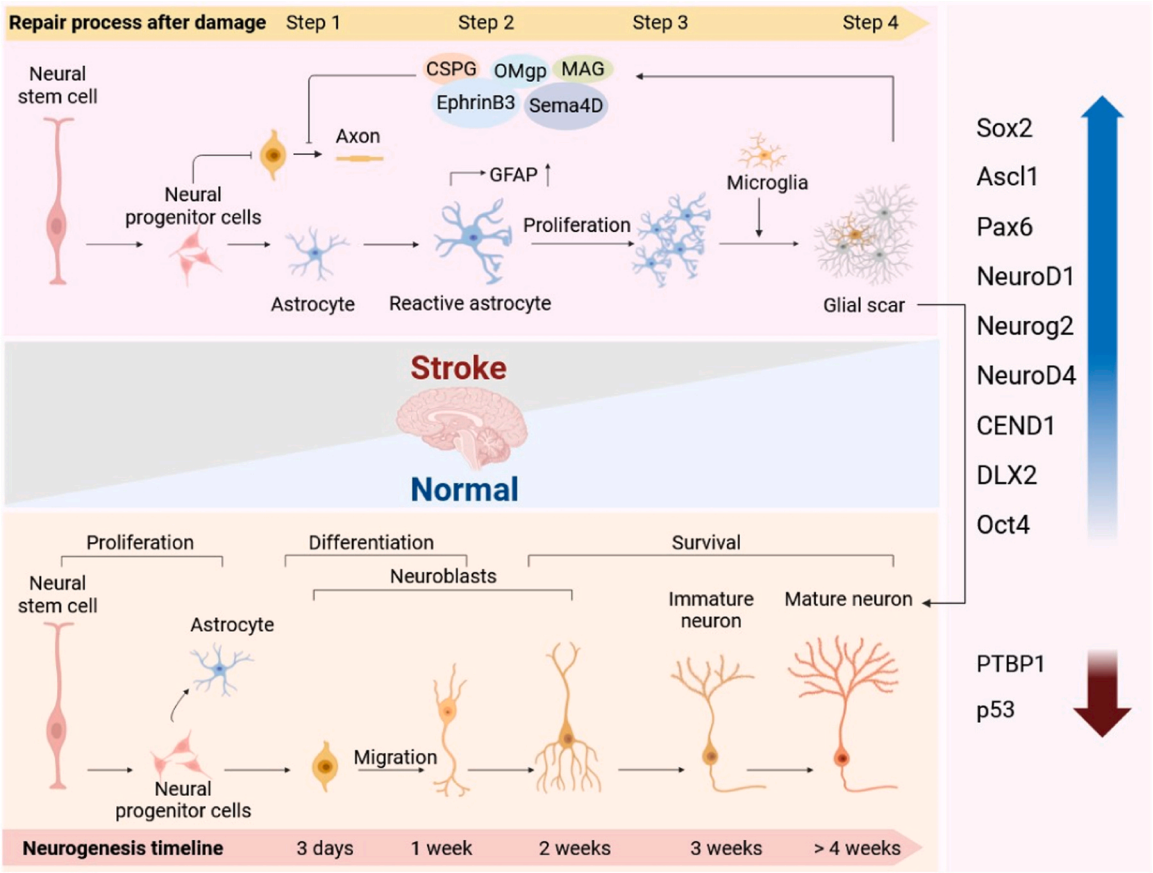

Fig. 1. The processes of neurogenesis under physiological conditions and in repair following CNS injury. During normal neurogenesis, neural stem cells differentiate into astrocytes and neural progenitor cells, the latter of which differentiate further into primary neurons after 3 days. These primary neurons subsequently migrate to their designated locations at 1 week where they gradually undergo maturation into immature neurons after 3 weeks and into mature neurons after 4 weeks. However, when the CNS is injured, such as during a stroke, astrocytes proliferate in large numbers and undergo a phenotypic switch to "activated" GFAP-positive reactive astrocytes, which are hyperproliferative; such astrocytes communicate with and drive the activation of microglia, leading to the formation of a glial scar that prevents the injury from expanding further. During glial scar formation, neuroinhibitory factors produced by reactive astrocytes, such as CSPG, MAG, OMgp, EphrinB3, and Sema4D, impede neuronal regeneration and axon formation as well as neurological functional repair after CNS injury. The key genes that have been shown to induce astrocyte-to-neuron differentiation after CNS injury are listed on the right. The reprogramming of glial cells into neurons can be induced by the downregulation of PTBP1 (Polypyrimidine tract-binding protein 1) and p53 or the upregulation of *Sox2, Ascl1, Pax6, NeuroD1, Neurog2, NeuroD4*, *CEND1, DXL2*, and *Oct4* expression. (CNS, Central nervous system; GFAP, glial fibrillary acidic protein; CSPG, chondroitin sulfate proteoglycans; MAG, myelin-associated glycoprotein; OMgp, oligodendrocyte-myelin glycoprotein; EphrinB3, ephedrineB3; Sema4D, Transmembrane semaphorin4D; Sox2, SRY-box transcription factor 2; Ascl1, Achaete-scute complex-like 1; Pax6, Paired box protein 6; NeuroD1, Neurogenic differentiation 1; Neurog2, Neurogenin2; NeuroD4, neuronal differentiation 4; CEND1, cell-cycle exit and neuronal differentiation 1; DLX2, distal-less homeobox 2; Oct4, octamer (ATGCAAAT)-binding transcriptional factor 4).

of cytokines, inflammatory factors, and inducing an imbalance of the redox state [6]. Studies have suggested that cell therapy may be a new treatment for neurodegenerative diseases [7] , reprogramming human pluripotent stem cells, fibroblasts, and astrocytes into neurons may hold great promise as a potential strategy for treating Parkinson's disease [8]. Therefore, inducing reactive astrocytes around the lesion instead of the normal astrocytes prevalent in the brain to reprogram neurons can promote neuronal regeneration and reconstruct the neural function network on the one hand, and maintain the normal function of astrocytes on the other hand, provide a microenvironment suitable for neuronal survival, and maintain brain homeostasis [9]. Reactive astrocytes are ideal cells for reprogramming into neurons because they retain the original morphology of the radial glia (RG) that neurons can be generated from [10]. In addition to reactive astrocytes, we note that NG2-positive glial cells also have the potential to be induced into neurons. NG2-positive cells, also known as oligodendrocyte precursor cells (OPCs), under in vitro conditions, NG2 cells exhibit pluripotent stem cell properties. They can differentiate into oligodendrocytes, astrocytes, and even neurons when stimulated by specific factors [11]. The study found that reactive astrocytes derived from NG2 cells could be detected in CNS-injured transgenic mice [12,13], and after spinal cord injury, NG2 cells are involved in scar formation [14]. Therefore, the induced reprogramming technique is also suitable for transforming NG2 cells into neurons to promote the recovery of neurological function after CNS injury. The feasibility of this idea has been demonstrated by the ability of NG2 cells to produce neurons [15,16], and by utilizing the neurogenic potential of NG2 cells to produce neurons after spinal cord injury, contributing to the recovery of neurological function after injury [17].

In addition, various studies have demonstrated that protocols targeting specific neural transcription factors such as SRY-box transcription factor 2 (*Sox2*), achaete-scute complex-like 1 (*Ascl1*), and paired box protein 6 (*Pax6*) are likely to be the main means through which neuronal reprogramming is induced (Fig. 1).

The reprogramming of reactive astrocytes into neurons primarily involves two approaches. The first approach is cellular dedifferentiation, in which astrocytes are induced to form neurospheres; subsequently, differentiation into neurons that exhibit typical neuronal properties [18]. The second approach is "transdifferentiation," also known as "direct cellular reprogramming," which involves the transformation of cells of one lineage into those of another through the reprogramming of somatic cells in response to specific factors; this process occurs more quickly and efficiently than does indirect reprogramming, as it does not require intermediate transition states. In principle, such reprogramming is more suitable for *in vivo* tissue repair than indirect reprogramming because it can occur *ex vivo* and *in situ* within the target tissue. In addition, direct reprogramming exhibits a greater capacity for preserving the epigenetic characteristics of the original (primitive) cells than indirect reprogramming [17], making it particularly suitable for reprogramming reactive astrocytes into neurons. Therefore, a great focus is placed on the process of direct reprogramming and its induction schemes.

Both astrocytes and neurons are derived from the neuroectoderm; however, the direction of differentiation is determined by the signaling pathways that are predominantly activated during the redifferentiation process. Therefore, the key to successfully inducing the reprogramming of astrocytes into neurons lies in activating the neuron differentiation-related signaling pathways while simultaneously inhibiting those associated with astrocyte differentiation; this can be achieved through the application of protocols that reduce neuronal apoptosis or other types of cell death after induction while maintaining their functional activity.

Currently, three main methods have been identified for inducing the direct reprogramming of reactive astrocytes into neurons. The first method involves the selection of transcription factors that promote neuronal differentiation during neurogenesis; the overexpression of such factors in astrocytes will alter their phenotype and function, facilitating their differentiation into neurons. However, the administration of a single neurotranscription factor has a limited influence on the conversion of astrocytes into neurons; therefore, subsequent induction protocols were developed to augment the efficacy of the transformation through the concurrent administration of multiple neurotranscription factors. Based on the functions of the various neurotranscription factors involved in neurogenesis, distinct combinations can be selected to facilitate the preservation of neuronal morphology and function to effectively enhance the astrocyte-to-neuron differentiation process. In practice, however, the selection of multiple neurotranscription factors poses a technical obstacle, as numerous transfections impede cellular survival. Furthermore, there is some controversy regarding the safety of utilizing retroviruses or adeno-associated viruses (AAVs) that carry multiple transcription factors in *in vivo* experiments. Thus, a third induction approach was developed to enhance conversion efficiency while simultaneously maintaining safety; this approach involves combining neurogenic transcription factors with small molecules to synergistically promote the differentiation of astrocytes into neurons. Several studies have confirmed that such an approach using a combination of small-molecule compounds can induce the direct reprogramming of astrocytes into neurons [19], creating new opportunities to improve the efficiency and safety of such conversions while also reducing the oncogenic potential.

Initially, small-molecule compounds were predominantly used as molecularly targeted drugs to induce therapeutic effects by inhibiting the proliferation and metastasis of malignant tumors [20–22], including those in the CNS. The clinical treatment of glioblastomas (GBMs), which can be triggered by the malignant proliferation of astrocytes [23], has remained challenging owing to the high levels of proliferation and the ease of recurrence of the disease [24], and immunotherapies such as those involving programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) as well as chimeric antigen receptor (CAR) T-cell therapy remain unoptimized due to the limited specificity and incomplete clearance of tumor cells [25]. Existing studies have shown that inducing the differentiation of tumor cells into normal cells, thereby inhibiting their proliferation and reducing their number, is likely to be a novel means of inhibiting tumor progression. Therefore, inducing astrocyte reprogramming into neurons may provide a new theoretical basis for GBM treatment.

The purpose of this review was to explore the feasibility of approaches for reprogramming astrocytes into neurons from a molecular biological perspective using several possible induction strategies. This review summarizes the small-molecule compounds that can be used to induce this type of cellular reprogramming. Additionally, it describes the superiority of combining the administration of neurotranscription factors with small-molecule drugs as new therapeutic strategies for promoting neural regeneration and the recovery of neurological function after CNS injury or for the reprogramming of GBM cells into neurons to compensate for the shortcomings and side effects of existing treatments.

2. The role of astrocytes and neurons in the CNS

Astrocytes and neurons are the primary cellular components of the CNS, playing important and complementary roles in maintaining brain function and performing tasks related to the regulation of energy supplies and cell signaling. Astrocytes are the most abundant type of glial cells in the brain, predominantly exerting trophic and support functions under normal physiological conditions [26]. Astrocytes control the uptake of glucose from blood vessels and store large quantities of glycogen, and the lactic acid broken down by astrocytes provides a source of energy for neurons during states of hypoglycemia or high neuronal activity. Astrocytes also regulate ion transport [27], including the movement of Ca^{2+}, K^{+}, Cl^{-}, HCO_3^{-}, and I^{-}, which helps in the maintenance of energy sources by regulating the extra-neuronal ionic environment. Astrocytes can increase their buffering capacity to maintain the intra- and extracellular pH balance and normal neuronal activity while participating in

complex signaling and pathological processes in the CNS. When lesions occur in the CNS as a result of stroke, trauma, tumor growth, or neurodegenerative diseases [28] or owing to inflammatory conditions [29], pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin one (IL-1) stimulate the proliferation and polarization of quiescent astrocytes into a reactive phenotype (A1 astrocytes). An increase in A1 astrocytes predominantly occurs during the early stages of injury [30]; these reactive astrocytes secrete inflammatory factors and neurotoxic mediators, which further aggravate CNS injury. However, astrocytes may also hinder axonal regeneration in the late stages of injury owing to glial scarring [31].

In contrast, the main functions of neurons are to receive, integrate, and conduct signals to transmit information[32]. In terms of subcellular components, the cytosol and dendrites are mainly responsible for receiving and integrating information, whereas the axon is mainly responsible for generating action potentials and integrating information, which is transmitted neurochemically across synaptic terminals to effector cells or other neurons. However, neurodegenerative diseases or neuroinflammation can impair the ability of neurons to regenerate, resulting in a deterioration of function and ultimately leading to neuronal death.

The limited ability for neurons to regenerate makes it difficult to restore neural function once the CNS has been damaged and a large number of neurons have died, which can have a severely negative impact on normal human life. Therefore, the application of cell reprogramming technology to induce astrocyte reprogramming into neurons could become an important therapeutic strategy for restoring neurological function after CNS injury.

3. Neurogenesis of astrocytes and neurons

3.1. Neurogenic processes

Neurogenesis begins with the proliferation of NSCs and the balanced and unbalanced divisions that lead to the formation of directed progenitor cells that gradually migrate toward functional regions where they undergo continuous plastic changes and establish synaptic connections with other neurons to generate neural functionality. The process begins with RG cells in the subgranular region of the embryo [33], which have a high capacity for expansion. These expanded cells are called progenitor cells, which will eventually divide asymmetrically to produce adult neurons; more specifically, they gradually migrate toward the granule cell layer and develop into immature granule neurons, after which they migrate toward the molecular layer to form mature granule neurons, which can then be integrated into the hippocampal circuitry to influence behavior. After birth, NSCs are present in the developing brain and continue to lead to the production of neurons, primarily in the subependymal ventricular zone (SVZ) in the lateral ventricular wall. These neurons migrate to the olfactory bulb, where they continuously replace localized interneurons. Neurogenesis also continues to occur in

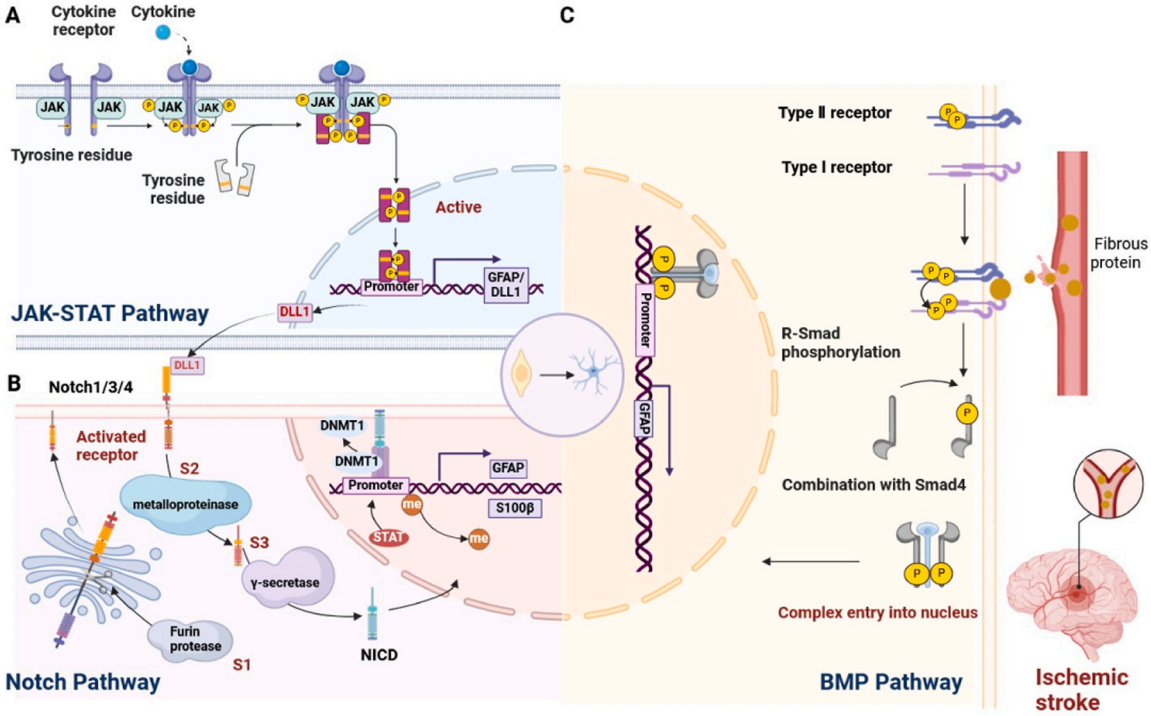

Fig. 2. The key signaling pathways and mechanisms that regulate the differentiation of NSCs into astrocytes. A: In the JAK-STAT signaling pathway, cytokines bind to receptors expressed on the cell membrane and mediate receptor dimerization. JAK binds to cytokine receptors on the cell membrane, exposing tyrosine binding sites and promoting their phosphorylation. The phosphorylated cytokine receptors recruit STAT, which binds to tyrosine residues on the receptor, allowing JAK to further mediate the phosphorylation of STAT. Phosphorylated STAT promotes dimerization and entry of the dimer into the nucleus. Intranuclear STAT binds to target gene promoters and promotes the transcription of target genes such as *GFAP* and *DLL1*. B: The Notch signaling receptor is transferred to the cell membrane after being sheared by Furin protease on the Golgi apparatus through a process known as S1 cleavage. DLL1 binds to Notch1/3/4, inducing binding between the Notch ligand and Notch receptor; this activates the Notch signaling pathway, causing the entry of the Notch protein into the cell. In which, the S2 and S3 cleavages are performed under the action of metalloproteinases and Γ-secretase, respectively, ultimately forming a Notch intracellular domain (NICD), which enters the nucleus and binds to the promoter region of the target gene. This results in the dissociation of DNMT1 from a target gene such as *GFAP*, thereby promoting its transcription; these changes are accompanied by the demethylation of the promoter region of a target gene such as S100ß and recruitment of the transcription factor STAT to promote its transcription. C: When an ischemic injury occurs, fibrous protein blood vessels become exposed, initiating a signaling cascade involving the activation of type II and type I serine-threonine kinase receptors, mediating receptor-activated R-Smad phosphorylation. R-Smad binds to Smad4 and enters the nucleus as an aggregator, binding to the promoter of a target gene such as *GFAP* and promoting its expression. (JAK, Janus kinase; STAT, signal transducer and activator of transcription; DLL1, Delta-like ligand 1; DNMT1, DNA methyltransferase 1).

the adult hippocampus, particularly in the subgranular layer (SGL) of the dentate gyrus [34]. Accordingly, both astrocytes and neurons are derived from the neuroectoderm; however, the direction of differentiation depends on the signaling pathways that predominate during the redifferentiation process. By understanding the signaling pathways that exert a regulatory role in the process of neurogenesis, the balance between astrocytes and neurons can be controlled by activating or inhibiting the function of one or more pathways.

3.2. Signaling pathways involved in the differentiation of NSCs into astrocytes

Various signaling pathways that play important roles in the differentiation of NSCs into astrocytes have been identified to date and are summarized in Fig. 2[35–40]. From late gestation to the perinatal period, NSCs give rise to astrocytes, and Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling plays a critical role in various developmental pathways, particularly in those that promote the generation of astrocytes [38]. During late gestation, a period that is associated with a decrease in basic helix-loop-helix (bHLH) expression levels, this signaling pathway is strongly activated and plays an important role in the generation of astrocytes [39]. This pathway can be activated by various proteins, including leukemia inhibitory factor (LIF), basic fibroblast growth factor (bFGF) [36], and members of the interleukin 6 (IL-6) family of cytokines. Upon receptor binding, JAK becomes autophosphorylated, resulting in its activation. Activated JAK, in turn, phosphorylates tyrosine residues on the intracellular structural domains of these receptors, where the signal transducer and activator of transcription 3 (*STAT3*) is recruited and phosphorylated by JAK; subsequently, phosphorylated STAT3 homodimerizes and translocates into the nucleus to induce the expression of astrocytic genes, such as glial fibrillary acidic protein (*GFAP*), thereby promoting astrocyte differentiation (Fig. 2A).

Notch signaling controls the direction of NSC differentiation in favor of astrocytes over neurons. To verify the mechanism of action of Notch, Tanigaki et al. [40] overexpressed Notch in pluripotent neural progenitor cells (NPCs) and found that activated Notch1 and Notch3 promoted astrocyte development by inhibiting neuronal and oligodendrocyte differentiation; they also observed that disrupting the binding of STAT3 to GFAP did not affect Notch-induced activation of *GFAP* transcription, suggesting that the Notch pathway regulates astrocyte differentiation in a matter that is independent of STAT3. Another study conducted by Kanski et al. [37] also demonstrated that the Notch signaling pathway regulates astrocyte differentiation in concert with the JAK/STAT pathway. In terms of the molecular mechanism, the interaction is mediated by STAT3, which induces Notch delta-like ligand 1 (DLL1); this results in the activation of Notch signaling in adjacent cells. Notch drives the differentiation of NSCs into astrocytes through the demethylation of astrocyte-specific genes. More specifically, the expression of the Notch intracellular domain (NICD) induces transcription of the GFAP promoter as well as the S100β demethylation of STAT3 binding sites within the promoter [35], and Notch activation leads to dissociation of DNA methyltransferase I (DNMT1) from the GFAP promoter, leading to its transcription (Fig. 2B).

Bone morphogenetic proteins (BMPs) are well-studied cytokines that induce the generation of astrocytes in neural stem/progenitor cells (NSPCs) during the late gestational period [41]. Numerous studies have demonstrated that BMP signaling promotes the differentiation of NPCs into astrocytes. Fibrinogen activates BMP type I receptors through binding to the αC structural domain, resulting in the activation of BMP signaling. Fibrinogen treatment of NSPCs induces the expression of BMP target genes, such as inhibitors of DNA-binding 1–3 (Id1–3), resulting in the activation of signal transducer Smad1/5 and the regulation of GFAP expression [42] (Fig. 2C). Circulating blood-derived fibrinogen induces the generation of astrocytes in ectopic brain stem cells [43] and inhibits the neuronal differentiation of primary NSPCs from the SVZ or hippocampal region, promoting their differentiation into astrocytes *in vitro*.

3.3. Signaling pathways involved in the differentiation of NSCs into neurons

Recently, several studies have focused on the neurogenic effects of Wnt family proteins, such as Wnt4, Wnt5a, and Wnt11. Non-classical Wnt signaling pathways, including the Wnt/Ryk, Wnt/Ca^{2+}, and Wnt/c-Jun N-terminal kinase (JNK) pathways, have been reported to play key roles in neural differentiation, with Wnt4 having been identified as a key effector molecule that promotes NSC-to-neuron differentiation during neurogenesis. Wnt4 promotes neuronal differentiation through the Wnt/β-linker protein and mitogen-activated protein kinase (MAPK)/JNK signaling, and Wnt4 inhibits the negative effects of Notch signaling in neuronal differentiation by suppressing Hes1 and Hes5 *in vitro* [44]. Additionally, the activation of the Wnt4 pathway significantly increases the expression of various neuronal markers, including β3-microtubulin, microtubule-associated protein 2 (MAP2), and neurofilament 200 (NF200) (Fig. 3), without altering the expression levels of the astrocyte marker GFAP.

In addition, Transforming growth factor beta (TGF-β) also promotes the development of dopaminergic neurons [45] and is involved in cell cycle exit and the initiation of neuronal differentiation, among other processes. Furthermore, endogenous TGF-β signaling may be active in both post-mitotic immature neurons and in mature neurons in the dentate gyrus [46]. Smad2/3 is an intracellular molecule that participates in the TGF-β signaling cascade, and several studies have shown that Smad2/3 is expressed in neuroblasts as well as immature and mature granule neurons, controlling the survival of intermediate progenitors and the rate of *denovo* neuron production in the adult dentate gyrus [47]. Deficiency of the TGF-β type I receptor, ALK5, results in a reduction in the number of doublecortin $(DCX)^{+}$ neurons, whereas activation of ALK5 promotes neuronal maturation (Fig. 3). Thus, TGF-β exerts neuroprotective effects and promotes neurogenesis in adults.

Glycogen synthase kinase 3 (GSK3), a key regulator of neurodevelopment, is widely expressed in the CNS, with particularly high expression levels in the hippocampus in all stages from embryonic development to adulthood. During the proliferative phase of neurodevelopment, the upstream signal protease-activated receptor 3 (Par3), as well as Wnt and Notch signaling, can inhibit GSK3, promote NPC proliferation, and impede neuronal differentiation. A previous study [46] demonstrated that during the late developmental phase, GSK3 phosphorylation degrades c-Myc/β-linker proteins, thereby inhibiting NPC proliferation and promoting neuronal differentiation. In a clinical study involving preterm infants [48], intraventricular hemorrhage led to damage of the cerebral cortex and detrimental effects on neurodevelopment, whereas GSK3β inhibition restored the process of neurogenesis and the number of neurons in the suprachiasmatic cortical layer.

Collectively, the results from the studies that have investigated related signaling pathways have led the authors to hypothesize that the inhibition of signaling pathways that promote astrocyte differentiation (e.g., those involving JAK/STAT, Notch, and BMP), as well as the activation of signaling pathways that promote the differentiation of NSCs into neurons (e.g., Wnt signaling), are key steps in optimizing the induction of neuronal reprogramming. This can be achieved through the application of specific small-molecule drugs, such as SP600125, which is a selective JNK pathway inhibitor, and the artificial overexpression of neuron-related neurotranscription factors could also be an effective means of inducing such reprogramming.

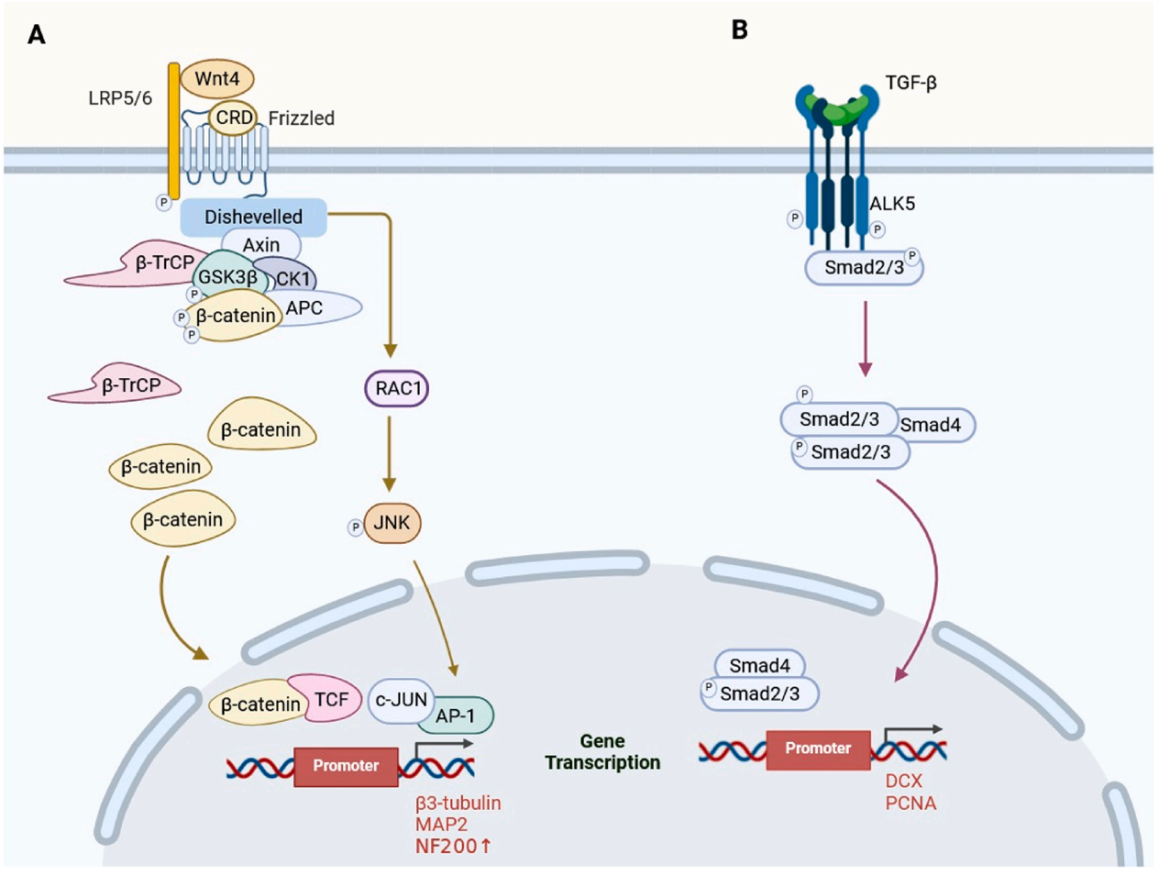

Fig. 3. The key signaling pathways and mechanisms involved in regulating of the differentiation of NSCs into neurons. A: Wnt4 binds to transmembrane proteins with a cysteine-rich domain before binding to the receptor through the extracellular N-terminal structural domain to activate the Wnt signaling pathway. When Wnt signaling is not activated, β-catenin exists within the cytoplasm in a phosphorylated form where it forms a complex with Axin, GSK3β, CK1, βTrCP, and APC. When Wnt signaling is activated, however, Dishevelled in the cytoplasm inhibits the formation of the complex, allowing β-catenin to exist in a free, dephosphorylated form. This form of β-catenin enters into the nucleus from the cytoplasm and binds to TCF (transcription factors) to induce the expression of downstream neuronal marker-related genes. (e.g., *β3-tubulin*, *MAP2*, and *NF200*). Dishevelled can also activate RAC1, which can, in turn, phosphorylate and activate JNK, which enters the nucleus where it can synergize with a variety of transcription factors (e.g., *c-JUN, AP1*), ultimately affecting the transcription of genes and resulting in the upregulated expression of *β3-tubulin*, *MAP2*, and *NF200*. B: Different activation modes of the TGF-β signaling pathway induce different directions of differentiation of neural stem cells. The TGF-β family cytokines induce serine/threonine kinase-type receptors on the cell membrane to form ALK5, a functional complex involving two type II receptors (RII) and two type I receptors (RI). RII receptors phosphorylate the GS region in the intracellular structural domain of RI, activating the kinase activity of RI; the phosphorylation of RI activates downstream Smad2/3, which subsequently polymerizes with Smad4 to induce the formation of the Smad complex, which enters the nucleus and binds to the promoter regions of target genes, regulating the expression of neuron-related genes such as *DCX* and *PCNA*. (LPR5/6, Low-density lipoprotein receptor-related protein 5/6; APC, Adenomatous polyposis coli protein; GSK3β, Glycogen synthase kinase-3β; MAP2, Microtubule-associated protein2; NF200, Neurofilament 200; DCX, Doublecortin; PCNA, proliferating cell nuclear antigen; RAC1, Ras-related C3 botulinum toxin substrate; JNK, c-Jun N-terminal kinase; TCF, Transcription factor; AP-1, activating protein-1; ALK5, TGF-β receptor type-1; TGF-β, Transforming growth factor beta; Smad, Signal transduction factor).

4. Cell reprogramming techniques for inducing astrocyte-to-neuron differentiation

4.1. Ectopic expression of transcription factors promotes the reprogramming of astrocytes to neurons

Since the first demonstration that the ectopic expression of transcription factors could alter the fate of somatic cells via cell lineage switching, an increasing number of studies have focused on the role of transcription factors in cellular reprogramming. Today, it was found that targeted inhibition of Notch1 signaling after spinal cord injury promotes the reprogramming of reactive astrocytes to neurons by upregulating neuro transcription factors such as *NeuroD1*, *Neurog2, and Pax6* [49] , overexpression of *NeuroD1* induces reprogramming of astrocytes into neurons in the brains of AD model mice [50], targeting specific transcription factors and miRNAs can induce the reprogramming of astrocytes into neurons in Parkinson's disease and play a therapeutic role [51]. This suggests that targeting specific neurotranscription factors is critical for achieving astrocyte reprogramming to neurons. This section will focus on existing neuronal reprogramming induction schemes, beginning with somatic cell reprogramming, with an emphasis on the neural transcription factors that play a prominent role in such processes.

4.1.1. Sox2

Sox2, a transcription factor containing a high-mobility group (HMG) box, belongs to the *SOXB1* subset of Sox genes [52]. It plays a critical role in nervous system development after embryogenesis. Increased Sox2 expression is often observed in undifferentiated NPCs, making it a useful marker of NSC characteristics [53]. *Sox2* controls the development of different brain regions at the NSPC level, thereby influencing the development of specific differentiated neuronal and glial cell types [54].

In addition, *Sox2* is associated with glial cell reprogramming, and it can promote reparative neurogenesis in Müller/RG cells after retinal injury in zebrafish [55]. Besides that, following spinal cord injury, *Sox2* induces the reprogramming of Oligodendrocyte precursor cells (OPCs,

NG2 glial cells) into early neurons and can promote neurological recovery [17]. After brain injury, retroviruses carrying *Sox2* have also been shown to induce the transformation of NG2 cells into neurons [56]. Similarly, the ectopic expression of reprogramming factors such as *Oct4, Sox2,* and Nanog Homeobox (NANOG) in astrocytes activates genetic programming in NSCs and induces the generation of cells expressing NSPC markers. $CD44^{+}$ mature astrocytes also undergo this lineage switching, giving rise to cells that express NSPC markers and subsequently undergo differentiation into neurons, astrocytes, and oligodendrocytes without passing through a pluripotent state [57]. Research suggests that a single transcription factor, *Sox2*, can reprogram astrocytes into proliferating neuroblasts. When neurotrophic factors or histone deacetylase inhibitors are applied in combination, neuroblasts transdifferentiated from astrocytes can further differentiate into mature neurons and functionally integrate into local neural networks [58]. The application of combination treatments that involve the neurotranscription factor *Sox2* and small-molecule drugs has also been shown to be effective in regulating reprogramming efficiency and progression.

4.1.2. Ascl1

In nervous system development, the generation and differentiation of neurons are dependent on a class of *bHLH* transcription factors known as proneural genes [59], which were initially discovered in Drosophila and named for their ability to regulate the differentiation of immature neuroectodermal cells into NSCs [60]. Subsequently, the proneural gene achaete-scute homolog 1 (*Ascl1*) was identified in mice [60–63], and its expression was later confirmed in NPCs in vertebrate species, as was its ability to induce neuronal differentiation, leading to further neuronal subtype characterization [64,65]. *Ascl1* was found to be critical for the generation of glutamatergic neurons in the hypothalamus during embryonic development [66].

Investigations into the role of *Ascl1* have revealed its ability to induce trans-lineage reprogramming [67]. For example, in studies investigating its role in somatic cell reprogramming, cells treated with *Ascl1* in combination with doxycycline induced the transformation of fibroblasts into neurons *in vitro*. [68,69], and the ectopic expression of *Ascl1* in neuroblastomas inhibited the expression of key transcriptional regulators that are known to be necessary for neuroblastoma proliferation, while simultaneously promoting the differentiation of neuroblastoma cells, inducing a shift from a proliferative neuroblast state to a state conducive to neuronal differentiation [70].

The role of *Ascl1* has also been investigated in mediating the reprogramming of astrocytes into neurons. As a proneural transcription factor, *Ascl1* can induce the reprogramming of early postnatal cortical astrocytes into actively conducting neurons capable of generating action potentials, which are characteristics of authentic neurons [71,72]. These effects of *Ascl1* may be related to the actions of Krüppel-like factor 10 (*Klf10*) and Myelin Transcription Factor 1 (*Myt1*), as neuronal differentiation 4 (*Neurod4*) and Chromodomain helicase DNA-binding protein 7 (*Chd7*) have been identified as key genes required for the efficient transformation of astrocytes into neurons [73]. Another study further investigated the role of *Ascl1* in mediating the transformation of adult astrocytes into neurons *in vivo*, showing greater neuronal transformation efficiency when six serine phosphorylation receptor sites in *Ascl1* were mutated to alanine (Ascl1SA6); thus, *Ascl1SA6* may be a key transcription factor for use in future studies [74].

4.1.3. Pax6

Pax6 plays an important role in cellular reprogramming. For example, the overexpression of *Pax6* in mouse embryonic stem cells induces their differentiation into retinal NPCs [75]. *Pax6* also plays a key role in regulating the neuronal subtypes involved in neurogenesis and in determining their ultimate fate. In addition, Pax6-positive RG cells in the cerebral cortex serve as progenitors of most glutamatergic neurons, and the absence of *Pax6* expression in embryonic stem cells results in the generation of Mash1-positive RG cells, which tend to differentiate into gamma-aminobutyric acid (GABA) neurons that express high levels of the neurotrophin receptor p75NTR and ultimately undergo rapid cell death [76].

As a transcription factor expressed during neurogenesis in the developing cortex, *Pax6* is a critical driver of telencephalon formation [77]. *Pax6* is also of interest for research focusing on the mechanisms of astrocyte neurogenesis, as experiments have shown that it is localized in RG cells. It influences the neurogenesis of embryonic cortical precursors during the neurogenic deficit period, while its overexpression in Pax6-negative cortical astrocytes induces their differentiation into neurons [77].

4.1.4. NeuroD1

The neurotranscription factor *NeuroD1* is a member of the bHLH family. NeuroD protein has been confirmed to be involved in the differentiation of neuroectoderm cells into neurons during neurogenesis, and it becomes transiently overexpressed when a subset of neurons ultimately differentiate into their mature form [78]. Studies have found that the ectopic overexpression of *NeuroD1* in Xenopus embryos promotes neurogenesis and induces the premature differentiation of NPCs, a process that is essential for the maturation of cerebellar and hippocampal granule neurons [78–81].

The earliest studies on somatic reprogramming into neurons found that the overexpression of *NeuroD1* could induce the reprogramming of fetal fibroblasts into neuron-like cells that exhibited typical neuronal morphology and marker expression [69]. Subsequently, some researchers who focused on inducing the transformation of glial cells into neurons have demonstrated that astrocytes located in the cerebral cortex of mice with a brain injury or Alzheimer's disease (AD) models could be directly reprogrammed into functional neurons when *NeuroD1* was overexpressed, and such cells were capable of integrating into the local neural circuitry. In addition to mouse models, *NeuroD1* can reprogram human cortical astrocytes into functional neurons [50]. Another study found that three transcription factors, *NeuroD1*, *Ascl1*, and LIM homeobox transcription factor 1 alpha (*LMX1A*), in combination with microRNA 218, could reprogram astrocytes into induced dopaminergic neurons both *in vitro* and *in vivo* [82]. In addition, NeuroD1-mediated *in situ* conversion of astrocytes into neurons can induce the regeneration of a large number of new functional neurons following ischemic injury, and AAV-based gene therapy involving *NeuroD1* was shown to induce neuronal regeneration and promote the recovery of injured neurons, significantly contributing to the restoration of neuronal function [83].

4.1.5. Neurogenin 2 (Neurog2)

Neurog2, which is expressed in hypothalamic tubercular progenitor cells, is another member of the proneural gene family [60]. It plays a key role in the neurogenesis of early-born neurons within the embryonic tubercular hypothalamus, with the process being arrested in its absence [84]. In contrast, the overexpression of NEUROG2 in human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) results in the rapid and efficient generation of excitatory neurons, and induces the formation of a network of inhibitory GABAergic neurons in hESCs. [85].

Further studies have explored the role of *Neurog2* in the transformation of astrocytes into neurons in greater detail. For example, experimental models that have employed AAV-mediated delivery systems to induce the single-factor overexpression of *Neurog2* in astrocytes have demonstrated that the majority of astrocytes could be successfully converted into neurons in multiple brain regions, as well as in the midbrain and spinal cord. In the midbrain, Neurog2-induced neuronal cells exhibit a neuron-like morphology, with similar electrophysiological characteristics, glutamatergic properties (approximately 60 % similarity), and the ability to form local circuits of synapse-like structures. In the spinal cord, studies have shown that both normal and lesion-derived astrocytes can be transformed into functional neurons via the ectopic expression of *Neurog2* alone, and healthy spinal cord-derived

Neurog2-induced neuronal cells respond to different afferent signals transmitted from the dorsal root ganglia (DRG), indicating that induced neurons are fully functional [86]. Another study reported that adult human cortical astrocytes can be directly reprogrammed by exposure to either cell-cycle exit and neuronal differentiation 1 (CEND1) or *Neurog2* into cells with the morphology of differentiated neurons, with long axons and dendritic branching. In that study, the neuronal marker genes were significantly upregulated, whereas astrocytic marker genes were downregulated, with the differentiation-induced neurons exhibiting GABAergic and glutamatergic/dopaminergic properties upon CEND1 and *Neurog2* overexpression, respectively [87].

4.1.6. NeuroD4

NeuroD4 is another protein that plays an important role in neuronal differentiation. The continuous expression of *NeuroD4* in adult and mouse cerebellar and hippocampal cells may be related to neuronal cellular regeneration [88,89]. In a study in which the overexpression of *NeuroD4* was induced in NSCs via a pseudotype retroviral vector with a neurotropic lymphocytic choriomeningitis virus (LCMV) envelope, NSCs were successfully transformed into neurons that exhibited the capacity for axonal regeneration. Additionally, such overexpression facilitated the differentiation of NSCs into both excitatory and inhibitory neurons while concurrently suppressing glial lineage-mediated scar formation, and the authors verified that the induced neurons were capable of forming functional synapses with neighboring cells [90].

As previously mentioned, *NeuroD4* can be used as a downstream target gene of *Ascl1* to induce the transformation of astrocytes into neurons capable of generating functional action potentials, and the reprogramming efficiency was shown to be stronger than that associated with the modulation of other genes downstream of *Ascl1* [73].

Another study reported that the regulation of *NeuroD4* itself was sufficient for the induction of neuronal reprogramming in astrocytes from both mice and humans, even without modulating upstream *Ascl1*, and co-expression with insulinoma-associated protein 1 (Insm1) further induced the formation of mature glutamatergic neurons; however, astrocytes gradually became resistant to such reprogramming. Although the mechanism responsible for such resistance was unclear, it was speculated to be partly attributed to the prevention of *Neurog2* binding to the *NeuroD4* promoter by the transcription repressor RE-1 silencing transcription factor (*REST*), thereby inhibiting *NeuroD4* expression [72].

In addition to the aforementioned transcription factors, many other genes play important roles in the reprogramming of astrocytes into neurons. For example, nuclear receptor-related 1 protein (*Nurr1*) and *Neurog2* efficiently target astrocytes to facilitate their reprogramming into neurons [10], and *CEND1* can induce the reprogramming of astrocytes into GABAergic neurons [87]. Downstream of *Ascl1, Klf10, Myt1, and* myelin transcription factor 1 like *(Myt1l)* are all also capable of inducing neuronal generation [73], and the ectopic expression of distal-less homeobox 2 (*Dlx2*) can induce the conversion of astrocytes into GABAergic neurons [91]. In addition, the splicing factor Polypyrimidine tract-binding protein 1 *(PTBP1*) has been confirmed to play a critical role in neuronal reprogramming. For example, genetic deletion of *PTBP1* in a Parkinson's disease model induced the differentiation of astrocytes into neurons, consistent with previous findings, confirming the important targeting role of *PTBP1* in neuronal reprogramming [92, 93].

Despite these positive findings, the methods used to induce neuronal reprogramming through the modulated expression of single genes are controversial. A study published in 2019 suggested that *NeuroD1* regulates epigenetic remodeling and induces the conversion of small glial cells into neurons, with potential implications for neuronal regeneration in the therapeutic management of degenerative diseases such as AD [94]; however, that study's findings were later challenged in 2022, with some scientists suggesting that the observed effects of *NeuroD1* were instead a result of the leakage of retroviruses [95]. As early as 2021, some laboratories believed that neither the overexpression of *NeuroD1* nor the genetic knockout of *PTBP1* could induce the transdifferentiation of astrocytes into neurons, with one study suggesting that the neurons thought to have been generated as a result of trans-differentiation were endogenous neurons that were already present in the body [96]. Subsequently, controversial questions arose about the effect of *PTBP1* in neuronal reprogramming, with several studies published in 2023 reporting a failure of *PTBP1* to induce astrocyte-to-neuron transformation and suggesting that the previous findings were false positives arising from carrier leakage [97–100]. Accordingly, a subsequent study argued that the knockout of *PTBP1* did indeed produce different phenotypes and that positive induction results required the simultaneous downregulation of *PTBP2* expression [101]. To verify the authenticity of the experimental results, different control groups should be established, and the source of the induced neurons should be traced more precisely. Such controversies surrounding the induction methods further highlight the limitations of strategies that are solely based on the regulated expression of individual genes. Strategies that modulate the expression levels of two or more genes are increasingly being recognized as a critical approach for the reprogramming of astrocytes into neurons, such as protocols involving the overexpression of *Oct4* coupled with *p53* silencing. Furthermore, such strategies combined with the co-application of small molecules can significantly enhance the efficiency of neuronal reprogramming and can even induce the formation of organ-like structures [102].

4.2. The role of small-molecule compounds and microRNA in the reprogramming of astrocytes into neurons

4.2.1. Small-molecule compounds

The integration of small molecules has long been explored in cell reprogramming, especially in the conversion of somatic cells to induced pluripotent stem cells. In those studies, the addition of small molecules not only improved the induction efficiency but also further reduced the potentially negative outcomes related to the c-Myc oncogene as well as the carcinogenicity of the induction protocol [103–105]. Subsequently, studies confirmed the ability of small-molecule compounds to induce the reprogramming of astrocytes into neurons [19]. More recently, a study found that the combined application of four small-molecule compounds (SB431542, RepSox, CHIR99021, and Y-27632) in an induction protocol resulted in the successful reprogramming of human cortical astrocytes into neurons through the overexpression of Oct4 and the silencing of *p53*, a strategy that was also capable of further inducing the generation of organoid tissues [102]. The criteria for the selection of small-molecule compounds for reprogramming protocols are predominantly based on the inhibition of signaling pathways that favor glial cell differentiation and the activation of neuron-related signaling pathways [106].

Small-molecule compounds that have been reported to be involved in cellular reprogramming include SB431542, LDN193189, CHIR99021, RepSox, Y-27632, forskolin, 24-diamino-5-phenylthiazole (DAPT), SB203580, TTNPB, Kenpaullone, Valproic acid (VPA), Smoothened agonist (SAG), purmorphamine, SP600125, GO6983, bromodomain and extra terminal inhibitor 151 (I-BET151), isoxazole 9 (ISX9), dibutyryl cyclic adenosine monophosphate (DBcAMP), and dorsomorphin [106–111]. Small-molecule compounds involved in the neuronal reprogramming process and their ability to induce the generation of positively expressed neuronal markers are listed in Table 1.

BMP2/4 as well as TGF-β1, which are involved in the TGF-β signaling pathway, are strong inducers of NPCs into astrocytes [115], whereas SB431542, LDN193189, and RepSox are inhibitors of the TGF-β signaling pathway that mainly target different processes in TGF-β signaling cascades. For example. LDN193189 and RepSox are both specific BMP1 receptor inhibitors that are capable of inhibiting TGF signaling pathway-mediated maturation at an early stage, whereas SB431542 mainly inhibits the TGF-β receptor, which, in turn, inhibits the phosphorylation and activation of downstream genes, preventing the signaling from occurring [116]. Activation of the p38/MAPK

Table 1
Small-molecule compounds for neuronal reprogramming.

Name	Function	Positive indicators	Cited
SB431542	ALK4\5\7 activity inhibitor	MAP2, TUJ1, PAX6, Nkx6.1, Olig 2, GAD67, VGLUT1, FOXG1	[102]
Y-27632	ALK5 inhibitor	MAP2, TUJ1, PAX6, Nkx6.1, Olig 2, GAD67, VGLUT1, FOXG1	[102]
CHIR99021	GSK-3α/β inhibitor	MAP2, TUJ1, PAX6, Nkx6.1, Olig 2, GAD67, VGLUT1, FOXG1	[102]
RepSox	ALK5 inhibitor	MAP2, TUJ1, PAX6, Nkx6.1, Olig 2, GAD67, VGLUT1, FOXG1	[102]
LDN193189	ALK2\3 activity inhibitor	NeuN, TUJ1, MAP2, SV2, FoxG1, Ctip2, Prox1, VGLUT1, DCX	[106]
DAPT	γ-secretase inhibitor	NeuN, TBR1, PVALB, CTIP2, VGLUT2	[106]
Forskolin	ALK5 inhibitor	MAP2, TUJ1 ，DCX, NeuN, SYN1, CHAT, VGLUT1, TH	[3]
SB203580	P38/MAPK inhibitor	MAP2, TUJ1 ，DCX, NeuN, SYN1, CHAT, VGLUT1, TH	[3]
Ruxolitinib	JAK1/2 inhibitor	MAP2, TUJ1 ，DCX, NeuN, SYN1, CHAT, VGLUT1, TH	[3]
TTNPB	RAR agonist	NeuN, Tuj1, MAP2, SV2, FoxG1, Ctip2, Prox1, VGLUT1, DCX	[106]
SAG	Smo receptor agonist	NeuN, TUJ1, MAP2, SV2, FoxG1, Ctip2, Prox1, VGLUT1, DCX	[106]
VPA	HDAC1 inhibitor	NeuN, TUJ1, MAP2, SV2, FoxG1, Ctip2, Prox1, VGLUT1, DCX	[106]
Kenpaullonec	GSK-3βinhibitor	Tuj1, MAP2, HB9, ISL1, CHAT, NeuN, SYN, VAChT	[107]
purmorphamine	Smo receptor agonist	TUJ1, MAP2, HB9, ISL1, CHAT, NeuN, SYN, VAChT	[107]
SP600125	JNK inhibitor	NeuN	[112]
GO6983	PKC inhibitor	TUJ1, DCX, NeuN, MAP2, GABA, VGLUT1	[113]
I-BET151	BET bromodomain inhibitor	NeuN, TBR1, PVALB, CTIP2, VGLUT2	[109]
ISX9	neural stem cell differentiation inducer	NeuN, TBR1, PVALB, CTIP2, VGLUT2	[109]
DBcAMP	PKA activator	NeuN, TBR1, PVALB, CTIP2, VGLUT2	[109]
dorsomorphin	AMPK inhibitor	Neurite-bearing cell	[114]

signaling pathway promotes astrocyte survival [117]. Therefore, some studies have used the p38/MAPK inhibitors SB203580 and RepSox as neuronal inducers, which effectively trigger the reprogramming of astrocytes into neurons [3].

In addition to small molecules that target specific components of signaling pathways, other effective small-molecule agents that function by maintaining cell survival are usually co-applied, thereby improving reprogramming efficiency; one such example is the GSK3 inhibitor CHIR99021, which is mainly used to maintain the homeostasis of NPCs and induce subsequent neural differentiation [118]. Other small molecules include the Rho-associated kinase (ROCK) inhibitor Y27632, which is used to promote cell survival and enhance reprogramming efficiency [119] and the γ-secretase inhibitor DAPT, which helps promote neural differentiation [120].

The co-application of small-molecule compounds greatly improves the efficiency of regimes intended for the reprogramming of astrocytes into neurons, and unique combinations could be used for further optimizing such protocols.

4.2.2. MicroRNA

In the previous introduction, we noticed that transcription factors combined with miRNA can induce the reprogramming of astrocytes into neurons under in vivo and in vitro conditions [82], indicating that miRNA also plays an important role in the reprogramming process. MicroRNAs (miRNAs) are a class of non-coding single-stranded RNA molecules of approximately 22 nt in length, which are involved in post-transcriptional regulation of gene expression [121]. Several miRNAs have also been shown to play a role in the transformation of astrocytes into neurons, including miR-302/367, miR-365, miR-124, and miR-21, among others. For example, in 2015 it was first demonstrated that microRNAs can transform astrocytes into neuroblasts. miR-302/367 co-administered with valproic acid (VPA), a histone deacetylation inhibitor, resulted in a high conversion of astrocytes into neuroblasts. This method transforms astrocytes into neurons without reprogramming to the pluripotent stage [122]. In an animal model of transient MCAO, increased levels of miR-365 inhibited the conversion of astrocytes to neurons. This was achieved by targeting *Pax6*. On the other hand, overexpression of *Pax6* negated the miR-365-mediated reduction of astrocyte-to-neuron conversion in the rat brain after MCAO. Furthermore, the knockdown of miR-365 enhanced *Pax*6-mediated astrocyte neurogenesis and reduced neuronal damage in the brain after ischemic stroke [90]. miR-124 not only regulates physiological and pathological neuronal differentiation in NSC but is also a potent driver of astrocyte to immature neuronal fate reprogramming transition. It can directly target the RNA-binding protein Zfp36L1 and inhibit Zfp36L1 neurogenic interactions, and in vivo experiments have demonstrated that miR-124 induces the direct conversion of responsive astrocytes into immature induced neurons (iN) [123]; miR-124 also interacts with the small molecules ruxolitinib, SB203580 and trichostatin to inhibit HES1 expression by targeting the Sox9-NFIA-HES1 axis to promote the conversion of reactive astrocytes to neurons and to maintain neuronal stemness and inhibit the transition to a differentiated state [3]. miR-21, a switch that regulates the polarization of reactive astrocytes, can promote the transformation of astrocytes to ASCs after acute ischemic spinal cord injury (iN). It can promote astrocyte polarization toward type A2, targeting glycoprotein precursor (Gpc6) and glial cell line-derived neurotrophic factor (GDNF) through the *STAT3* signaling pathway to promote synapse formation and synapse growth [124]. These studies suggest that microRNAs are not only involved in neuronal maturation, growth, and synapse generation but also play an important role in promoting the transformation of astrocytes into neurons.

5. Prospects for reprogramming techniques for the treatment of CNS injury and GBM

5.1. Neurological recovery following CNS injury

CNS injury leads to primary or secondary neuronal damage or death, as well as axonal degeneration [125], resulting in both structural and functional damage to the nervous system. Owing to the production of factors that inhibit neuronal growth near the site of injury, the local pathological microenvironment is not conducive to nerve regeneration, and it is difficult to generate new neurons and axons after a CNS insult. The growth of axons of central neurons is typically limited to protrusions following injury, after which a retractile bulb is formed at their extremities, which prevents the axon from traversing the injury site and ultimately leads to regeneration failure. In addition, astrocytes located around the lesion are stimulated and transform into Reactive astrocytes (RACs) [126], forming a hard gelatinous scar that hinders axonal growth. Furthermore, cytokines produced at the site of injury, such as CNS myelin [127], chondroitin sulfate proteoglycans (CSPGs) released by RACs from the formation of a glial scar [128], myelin-associated glycoproteins (MAGs) derived from oligodendrocytes and myelin debris [129], Nogo proteins [130], oligodendrocyte myelin glycoprotein (OMgp) [130], EphrinB3, and semaphorin 4D (Sema4D) [131] have all been identified as factors that inhibit axonal regeneration.

Advances in cellular reprogramming technology are expected to provide fundamental solutions to overcome these unfavorable factors. In addition to directly inducing the transdifferentiation of astrocytes into

neurons, the process not only provides a means of generating newly born neurons and solving the problems associated with neuronal regeneration, but the application of reprogramming technology also further reduces the generation of glial scarring and the secretion of inhibitory cytokines that occurs in the later stages following CNS injury, facilitating the formation of a local microenvironment that provides favorable conditions for nerve regeneration and axon reconstruction, promoting functional recovery after injury.

5.2. Current and emerging therapeutic strategies for gliomas

Gliomas are the most common type of CNS tumors requiring neurosurgery and are the most frequently encountered cranial tumors in terms of their incidence. Gliomas can occur in all regions of the brain, including in the cerebellum or brainstem, although they primarily occur at the junction of the cortex and white matter, and they can be classified as astrocytomas (including GBMs), oligodendrogliomas, and mixed gliomas, among several other types, including gliomas of the optic nerve and brainstem [132]. Most gliomas originate from the malignant proliferation of astrocytes, especially GBMs, the most malignant form [133–135]. Therefore, starting from the characteristics of astrocytes to find treatment options for glioma provides a new perspective for improving patient prognosis.

Currently, there are three main treatment options for individuals with gliomas (surgical resection, chemotherapy, and radiotherapy); however, most treatment regimens involve a combination of these methods. The preferred treatment remains radical surgical resection; however, surgery for the removal of brain tumors is the most difficult surgical procedure, and it can be further complicated by the fact that gliomas do not have distinct boundaries and not all tumor cells can be completely removed. Therefore, chemotherapy is one of the most important treatment options for gliomas, which can include the use of agents such as temozolomide (TMZ) and bevacizumab (BEV) [136]. However, there is evidence of hypermutation, malignant transformation, and DNA mismatch repair (MMR) defects following treatment with chemotherapeutic agents [137], and there is still controversy regarding whether progression-free survival can be prolonged with such treatment [138]. In addition, a long-standing problem in the treatment of brain diseases that are reliant on systemic therapy is the presence of the blood–brain barrier (BBB), which limits the passage of chemotherapeutic agents into target tissues, reducing the efficacy of treatment [139] and isolating the CNS from the peripheral immune system [140]. Prolonged chemotherapeutic regimens lead to chemoresistance as well as the incomplete obliteration of tumor cells, increasing the likelihood of tumor recurrence. Although radiotherapy is another important treatment option for some individuals with gliomas, the rapid growth of such tumors can decrease the sensitivity to radiotherapy; thus, large doses of radiotherapy are needed to achieve the desired effect, which can also increase undesirable side effects and result in greater brain damage (Fig. 4A). Therefore, the identification of novel therapeutic strategies is urgently needed, in addition to the traditional surgical and chemo radiotherapeutic approaches to overcome the current challenge associated with glioma treatment.

The aforementioned limitations have led to the development of immunotherapeutic approaches to glioma treatment becoming a hot topic in current medical research, some of which have been successfully applied in clinical settings, such as the application of PD1/PD-L1, lysovirus therapy, and CAR T-cell therapy. However, it is still difficult to eliminate all tumor cells to prevent recurrence, as such approaches induce the activation of inflammatory signaling in vivo, which can negatively impact the function of other organs while attempting to promote CNS repair, and the highly tumor-immunosuppressive microenvironment and the evasion mechanisms tumors adopt to avoid immune system detection can negatively affect the therapeutic efficacy [141] (Fig. 4A). Therefore, new therapeutic approaches are required to further improve the treatment of gliomas.

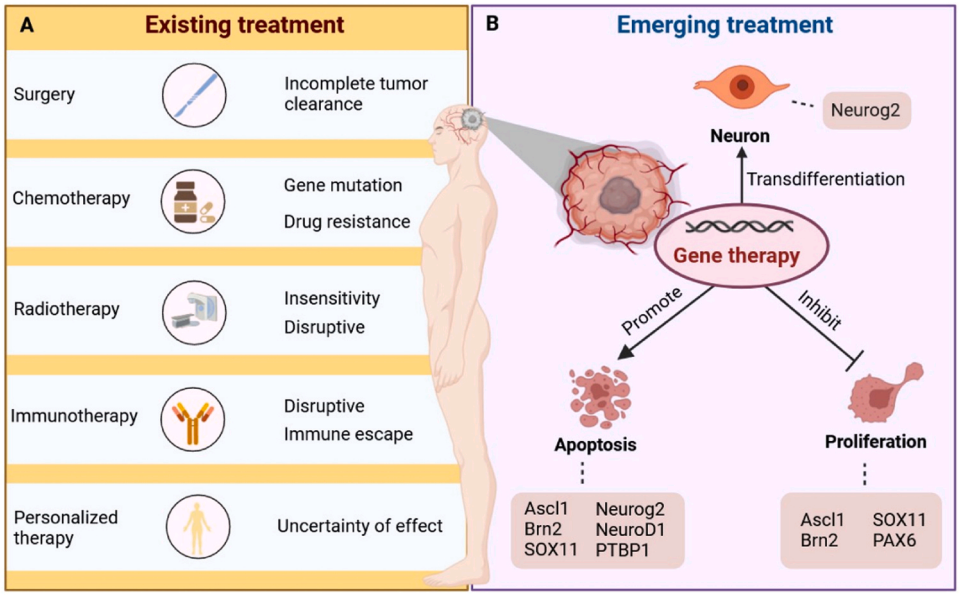

Fig. 4. Current and emerging therapeutic strategies for gliomas. A: Current treatment options for gliomas include surgery, chemotherapy, radiotherapy, and immunotherapy. Surgery is the most basic treatment strategy; however, it does not eliminate all tumor cells. TMZ and BEV are commonly used chemotherapeutic agents; however, their administration can cause genetic mutations and promote the development of chemoresistance. Radiotherapy can lead to off-target damage to normal cells, and the sensitivity of gliomas to radiation remains questionable. Immunotherapies based on PD1/PD-L1, oncolytic viruses, and CAR T-cell therapy are limited by immune escape. Although some personalized treatments are available, they are mostly palliative. B: The emerging treatment strategies for gliomas mainly involve gene therapy, including those that promote tumor cell apoptosis by inducing the ectopic expression of Neurog2 and those that induce the transformation of tumor cells into functional neurons by regulating the expression of Ascl1, Brn2, Neurog2, SOX11, NeuroD1, and PTBP1. Alternatively, Pax6, Ascl1, Brn2, Neurog2, and Sox11 can be used to inhibit tumor cell proliferation. (Ascl1, achaete-scute family bHLH transcription factor 1; BEV: bevacizumab; Brn2, POU class 3 homeobox 2; CAR, chimeric antigen receptor; NeuroD1, Neurogenic differentiation 1; Neurog2, neurogenin 2; Pax6, paired box protein 6; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTBP1, Polypyrimidine tract-binding protein 1; SOX11, Sex Determining Region Y-Box 11; TMZ: temozolomide).

Recent studies have shown that promoting the differentiation of tumor cells into normal non-tumor cells, thereby inhibiting their proliferation and reducing their number, could be a new and unique treatment method with the potential to halt tumor progression. Inducing astrocyte-derived glioma cells to differentiate into normal astrocytes or directly into neurons seem to be viable options, as existing studies have proven that GBM cells can be induced into neurons. However, astrocytes appear to be pro-carcinogenic, and not an ideal choice; therefore, an increasing number of studies have focused on inducing the differentiation of glioma cells into neurons [142,143].

5.3. Theoretical feasibility of reprogramming glioma cells into neurons

Based on the etiology of glioma cells, the first step in reprogramming strategies is to induce glioma cells to restore their astrocytic properties. However, GBM cells produce receptor activator of nuclear factor kappa B (NF-κB) ligand (RANKL), which activates the NF-κB signaling pathway, thereby promoting the proliferation and activation of astrocytes into tumor-associated astrocytes (TAAs), which subsequently produce pro-tumorigenic factors, such as TGF-β, that are known to enhance the invasive ability of GBM cells [142,144,145]. Meanwhile, it has been reported that TAAs induce an anti-inflammatory response that triggers an immunosuppressive environment and impedes the efficacy of immunotherapy, while glioma and microglia synergize to further promote astrocyte activation, creating a vicious circle [145]. Due to the interaction between TAAs and GBM, it is relatively difficult to convert GBM cells into normal astrocytes. On the one hand, under in vivo conditions, the transformation of GBM cells into astrocytes may be prevented due to the presence of TAAs. In addition, it is difficult to determine whether the astrocytes transformed by GBM cells are normal cells, resulting in that the transformed astrocytes may not have normal physiological functions. Finally, the abnormal astrocytes transformed by GBM cells may also be transformed into TAAs under the stimulation of the local tumor microenvironment, which further promotes the proliferation and immune resistance of GBMs, and the formation of a positive feedback communication between TAAs and GBM cells in the tumor local area aggravates the progression of the tumor.

To address these issues, some researchers have proposed strategies that promote the direct differentiation of GBM cells into neurons rather than relying on the intermediate generation of astrocytes that must undergo further reprogramming. Neurons, which are terminally differentiated, non-proliferating cells, are better targets for transformation than proliferating astrocytes and inducing the direct differentiation of GBM cells into neurons can greatly preserve neurological function in the brain, facilitating the recovery from the neurological dysfunction caused by tumor invasion during tumor treatment.

5.4. Research progress on the reprogramming of GBM cells into neurons

Gene therapy studies for the treatment of gliomas are increasingly being conducted to address the existing therapeutic bottlenecks. Given that astrocytes are capable of reprogramming into neurons, most studies have focused on exploring protocols that induce this type of trans-differentiation.

For example, the neuro-transcription factor *Pax6*, which is capable of inducing the reprogramming of astrocytes into neurons, could also inhibit the growth of GBM cells [146], and a subsequent study based on this finding reported that a combination of three transcription factors, *Ascl1*, POU class 3 homeobox 2(*Brn2)*, and *Neurog2*, could efficiently transform human glioma cells into functional neurons while inhibiting the proliferation of glioma cells [147]. Neuron formation is regulated by neurogenic transcription factors such as *Neurog1/2* and *NeuroD1*, which another study demonstrated were barely expressed in GBM cells; therefore, after constructing GBM cells that did express *Neurog2*, the authors found that there was an increase in GBM cell death, and the surviving cells exhibited evidence of neuronal morphology, with upregulated expression of the neuronal markers DCX and *NeuroD1* expression and the ability to generate action potentials [148]. Another group showed that the synergistic effects of *Neurog2* and *Sox11* effectively transformed human glioma cells into terminally differentiated neuron-like cells with a typical neuronal morphology that was accompanied by the expression of neuronal markers and the presence of electrophysiological properties, and the proliferation and development of GBM was inhibited [149]. The previous section mentioned that the ectopic expression of *Ascl1* in neuroblastoma cells was shown to induce their trans-differentiation into neuronal cells, and the same effect has been confirmed in terms of the shift from GBM cells. The single neuro-transcription factor *Ascl1* promotes the reprogramming of GBM cells into terminally differentiated neurons that exhibit typical neuronal morphology and expressed neuronal markers, a process that was mediated through the inhibition of Notch signaling; similarly, this process induces cell cycle exit in GBM cells and inhibits their proliferation [143, 150]. Therefore, the combination of *NeuroD1*, *Neurog2*, and *Ascl1* further improved the efficiency of this conversion to neurons, and neurons produced in response to the administration of *NeuroD1* and *Neurog2* behaved as excitatory glutamatergic neurons, whereas those produced through the administration of *Ascl1* behaved as inhibitory GABAergic neurons [151]. In addition, the knockdown of the shear factor PTBP1 induces a similar differentiation of GBM cells into neurons [152] (Fig. 4B). Besides, it is worth exploring that AAV-NeuroD1 induced neural reprogramming was reported to be the first AAV treatment for GBM in humans very recently, completed by NeuExcell Therapeutics, a study that took transcription factor-based gene therapy from theory to reality. However, the available data are still insufficient to support the use of AAV-NeuroD1 as a clinical treatment. There is still a lack of enough evidence on primates to treat GBM, and extensive phase III clinical trials are still needed to assess the safety of the AAV-NeuroD1 treatment and the stability of its efficacy. In addition, the controversy over AAV-NeuroD1 persists, and the safety and immune rejection of the AAV virus itself, the authenticity of the positive results, and the side effects of this kind of drug therapy still require continued attention. In the above studies, the cell lines selected were all astrocyte-derived glioma cell lines, such as U87, U251, and KNS-89. And the target factors used to reprogram GBM cells into neurons largely overlap with those used to reprogram astrocytes into neurons. It is speculated that the induction protocol targeting the transformation of astrocytes into neurons is also effective in reprogramming astrocyte-derived glioma cells into neurons. Subsequent research can further develop safer induction strategies on this basis, such as combining neural transcription factors with small molecule compounds. In this process, it has been found that the combination of small molecule compounds, cAMP inhibitors and HDAC inhibitors, can induce the transformation of glioma cells into neurons via the histone post-translational modification pathway, which effectively inhibits tumor proliferation and has a higher safety profile [153]. In addition, the study has found that the use of GSK3β inhibitors combined with TMZ can effectively inhibit GBM proliferation [154]. Therefore, to address the issues of viral vectors as well as transformation efficiency, and in conjunction with existing studies, this review suggests that transcription factors in combination with small molecule drugs are alternative induction regimens.

Small molecules and chemotherapeutic agents can also play an important role in promoting the conversion of GBM cells into neurons. For example, the administration of a combination of fasudil, Tranilast, and TMZ induces the reprogramming of human GBM cells into neuron-like cells that express neuronal marker genes and possess electrophysiological properties [155], and a small molecule cocktail consisting of forskolin, ISX9, CHIR99021, I-BET 151, and DAPT can successfully reprogram U87 cells into neurons [156], further confirming the importance of small molecules in cellular reprogramming. Interestingly, we found that the small molecule drugs and their combinations that induced the reprogramming of GBM cells into neurons were highly similar to those used during the reprogramming of astrocytes into

neurons. This suggests that fully exploring the induction strategies of astrocyte-to-neuron reprogramming could help develop more effective protocols for the transformation of GBM cells into neurons.

6. Forecast

The emergence of cellular reprogramming technologies has enabled the development of novel treatments for various diseases, and the reprogramming of astrocytes into neurons offers a promising approach for promoting regeneration following CNS injuries and for restoring neural function in various neurodegenerative conditions. Despite this, the outcomes of these induction strategies have remained controversial, regarding whether inadvertent contamination from the extraction process was responsible for the presence of the neuron-like cells that were transdifferentiated from astrocytes. In addition, some experimental findings have led researchers to challenge the presumed role of certain transcription factors in these processes, with some suggesting that leakage of the viral vector me be responsible for inducing neuronal production. To address these issues, tracing the exact origins of the apparently induced neurons without interference from viral vectors is an essential priority. In addition, the field remains limited by the challenges associated with explicitly targeting gene regulation, screening specific drug combinations, enhancing the production or delivery of viral vectors, and validating positive results.

Moreover, based on previous studies that have suggested that GBM cells can originate from astrocytes, research should focus on methods that facilitate the direct reprogramming of GBM cells into neurons to alter the characteristics of tumor cells, induce their cell death, suppress their proliferation, and restore neural functions. Although such approaches could lead to new therapeutic options for the treatment of GBM, several primary challenges must be overcome to optimize the reprogramming of astrocytes or GBM cells into neurons in terms of conversion efficiency and safety. It remains a possibility that some fraction of GBM cells cannot undergo effective reprogramming into neurons, meaning that some residual tumor cells could remain after treatment. Therefore, it will be important to further enhance the conversion efficiency and guarantee the complete elimination of tumor cells to minimize the likelihood of recurrence and optimize clinical outcomes while minimizing the impact of treatment on non-tumor cells. To cope with this problem, combined with the existing studies, we believe that choosing a suitable carrier to carry the drug is the best optimization solution. Exosomes are a class of extracellular vesicles with a diameter of about 100 nm. It has been found that exosomes can deliver siRNAs, microRNAs, and chemotherapeutic agents, and are considered to be the leading candidates for cancer therapeutic delivery vehicles [157]. It is hypothesized that small molecule compounds delivered via exosomes may be able to target tumor tissues, practice precise neuronal reprogramming, and greatly improve the efficiency of neural reprogramming. Combining cell reprogramming techniques with existing clinical treatments (such as radiotherapy), can help to further improve patient survival and prognosis. Cell reprogramming technology provides new treatment options for GBM patients.

It is well known that tumor cells undergo glycolysis function, which produces a large amount of lactic acid, putting the tumor cells in a high-lactic acid microenvironment [158]. The tumor microenvironment is closely related to tumor properties, and glioma is no exception. However, most of the current studies targeting the reprogramming of glioma cells into neurons have not taken into account the effects of lactate. In addition to cellular reprogramming, cyclin-dependent kinase inhibitor 2 A (CDKN2A) mediated lipid reprogramming, mechanistic target of rapamycin kinase (mTOR)-mediated metabolic reprogramming, and bromodomain containing 8 (BRD8)-mediated epigenetic reprogramming can induce tumor cells to enter a non-proliferative state, which in turn inhibits tumor proliferation and invasion [159–161]. Problems in transformation efficiency and multiple aspects of existing induction protocols may be due to the neglect of the role of the microenvironment and the neglect of the connections between other biological processes. At the same time, linking cellular reprogramming with metabolic reprogramming and epigenetic reprogramming is expected to further improve reprogramming efficiency and patient survival rates, as well as delay the progression of cancer.

Although astrocytes can proliferate in the CNS, their regeneration occurs slowly, and converting a large number of astrocytes into neurons could potentially deplete their populations in the CNS, which could have a detrimental effect on neural system function and raise concerns about the resultant potential harm to humans. Therefore, determining the optimal transformation multiplicity while simultaneously enhancing the transformation efficiency and controlling the impact of any residual drugs on the transformation procedure following discontinuation of the induction scheme are technical obstacles that must be resolved. To enhance the conversion efficiency, most researchers have focused on inducing combinations of genes and using small molecules that target specific signaling pathways involved in neurogenesis. Therefore, the neural reprogramming technique mentioned in this review aims to specifically induce the transformation of RAs into neurons by focal in situ injection of inducing reagents in the injured or lesion area, rather than inducing the neural differentiation of normal astrocytes in the whole brain through blood administration of inducing reagents, for example. Although the reprogramming techniques of RAs for neural differentiation need to be further improved, through this method we could precisely manipulate neural regeneration and remodeling in the lesion area, which is eventually beneficial to reducing glial scar and enhancing neural functional recovery.

Following CNS injury, neurons are damaged and their ability to regenerate is limited, whereas a large number of astrocytes undergo proliferation, which is the main factor hindering nervous system recovery. Therefore, reprogramming astrocytes into neurons may help replenish damaged populations and restore neural functions. This review discussed the feasibility of strategies for reprogramming astrocytes into neurons from the perspective of neurogenesis, with a focus on the key pathways, transcription factors, and small-molecule compounds involved in neuronal reprogramming and the associated mechanisms of action. In doing so, it provides an up-to-date reference that summarizes the existing research on nervous system repair post-injury. The discussion of the feasibility and research progress on the reprogramming of GBM cells into neurons will highlight the shortcomings of existing glioma treatment methods and provide new ideas for the treatment of GBM that will improve clinical outcomes.

Ethics approval statement

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Consent for publication

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CRediT authorship contribution statement

Meiying Li: Funding acquisition, Conceptualization. **Guangfan Chi:** Writing – review & editing, Funding acquisition, Conceptualization. **Qi Yu:** Investigation. **Haokun Li:** Writing – review & editing. **Junyuan Wei:** Writing – original draft, Software. **Shilin Li:** Formal analysis. **Miaomiao Wang:** Visualization. **Wenhong Xu:** Writing – review &

editing. **Anqi Zhao:** Visualization. **Rui Han:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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