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Review Article

Directed glial differentiation and transdifferentiation for neural tissue regeneration

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ABSTRACT

Glial cells which are indispensable for the central nervous system development and functioning, are proven to be vulnerable to a harmful influence of pathological cues and tissue misbalance. However, they are also highly sensitive to both in vitro and in vivo modulation of their commitment, differentiation, activity and even the fate-switch by different types of bioactive molecules. Since glial cells (comprising macroglia and microglia) are an abundant and heterogeneous population of neural cells, which are almost uniformly distributed in the brain and the spinal cord parenchyma, they all create a natural endogenous reservoir of cells for potential neurogenerative processes required to be initiated in response to pathophysiological cues present in the local tissue micro-environment. The past decade of intensive investigation on a spontaneous and enforced conversion of glial fate into either alternative glial (for instance from oligodendrocytes to astrocytes) or neuronal phenotypes, has considerably extended our appreciation of glial involvement in restoring the nervous tissue cytoarchitecture and its proper functions. The most effective modulators of reprogramming processes have been identified and tested in a series of pre-clinical experiments. A list of bioactive compounds which are potent in guiding in vivo cell fate conversion and driving cell differentiation includes a selection of transcription factors, microRNAs, small molecules, exosomes, morphogens and trophic factors, which are helpful in boosting the enforced neuro-or gliogenesis and promoting the subsequent cell maturation into desired phenotypes. Herein, an issue of their utility for a directed glial differentiation and transdifferentiation is discussed in the context of elaborating future therapeutic options aimed at restoring the diseased nervous tissue.

1. Introduction

Ontogenetic development and the physiological functioning of the central nervous system (CNS), as well as the initiation of the resulting neurorestorative processes entirely rely on multidirectional interactions between neurons and glia. Over the past few decades of a great deal of investigation on glial cells has enhanced the understanding of the multiple roles they play in the nervous tissue. Glia, which functions nowadays are regarded as going far beyond being just a “glue”, comprises the populations of macroglia and microglia. The former corresponds to the cells that originate from the ectoderm and are referred to as astrocytes, oligodendrocytes and ependymal cells, while the latter-the resident microglial cells-are derived from the yolk sac and populate the CNS during its early embryonic development (Hoeffel and Ginhoux, 2018; Lloyd et al., 2017; Rowitch and Kriegstein, 2010). As they play pleiotropic roles in the nervous tissue, glial cells were until some years ago thought to vastly outnumber neurons. However recent studies based on an innovative counting method employing an isotropic fractionator have allowed calculating the glia to neuron ratio being close to 1:1, with a total number of about 100 billion glial cells in the human brain (von Bartheld, 2017; García-Cabezas et al., 2016). In human spinal cords, the other part of the CNS rich in white matter, the same method estimated amount of glia for 1.5-1.7 billion cells and approximately 200 million neurons (which corresponds to 13.4% neurons, 12.2% endothelial cells, 74.8% glial cells, respectively), making the glia-neuron ratio oscillate between 5.6-7.1 (Bahney and von Bartheld, 2018). The proportion of neurons to glia seems to be precisely regulated to ensure efficient support of energetic substrates, as well as delivery of instructive signals and trophic factors, altogether contributing to the effective functioning of the CNS. Injury to the nervous tissue usually

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triggers a diversified response of glial cells, including their proliferation, migration, change in their secretome profile, and even de- or transdifferentiation aimed at initiating or enhancing endogenous processes associated with tissue repair.

2. Origin of glia during ontogenesis and in adulthood

Multipotent radial glia, which are perceived as primary neural stem cells (NSCs) and common precursors of both neurons and macroglia, originate from the neuroepithelial cells that line the cerebral ventricles and the spinal canal (Noctor et al., 2002; Rowitch and Kriegstein, 2010). Within the boundaries of the developing nervous system, the composition and concentration gradients of extrinsic instructive signals within the extracellular milieu play a crucial role in adopting cell fate by generated progenitors. The first pivotal morphogenic cues are derived from the ventral floor plate (Sonic hedgehog, Shh) and dorsal roof plate of the emerging neural tube (Bone morphogenetic protein, BMPs and WNTs) and are thought to exert opposite effects on promoting the expression of patterning molecules, which direct progenitor commitment and differentiation (Fuccillo et al., 2006; Sur and Rubenstein, 2005; Ulloa, 2010). Accordingly, the changing gradient of priming signals results in establishing regionally restricted domains of the neural tube (distinguished -from ventral to dorsal-as p3, pMN, p2-0 and dP6-1). During early neurogenesis, those regionally specialized domains contribute to derivation distinct subtypes of neurons, due to the transient expression of proneural basic helix–loop–helix factors, which function as patterning molecules (Le Dréau and Martí, 2012). Also within the developing forebrain, specialized regions are distinguished by gradients of organizing signals which emanate from specific centers and determine neural cell fate.

As embryogenesis proceeds, the changing composition of microenvironmental cues results in promoting the expression of gliogenic factors. In this way, the process of intense neurogenesis is followed by a period of active gliogenesis, resulting in generating astrocytes which populate the developing nervous system. They adopt one of two typical phenotypes: fibrous astrocytes can predominantly be found within the future white matter, while those characterized by the protoplasmic phenotype mainly inhabit the grey matter. These glial cells provide both structural and trophic support for generated neurons, regulate synapse formation, as well as participate in forming and maintaining the blood-brain barrier through life-span (Diniz et al., 2012; Hama et al., 2004; Ullian et al., 2001). The subsequent step of the tightly regulated process of gliogenesis is recognized by a switch to oligodendrocyte progenitor generation due to the expression of lineage-specific transcription factors like PAX6, OLIG2, NKX2.2 and NKX6.1/6.2 (reviewed by Küspert and Wegner, 2016). There is now a general consensus, that oligodendrocyte progenitor cells (OPCs) are generated in three waves along the ventral-dorsal axis (Kessaris et al., 2006; Sanchez and Armstrong, 2018; van Tilborg et al., 2018; Vallstedt et al., 2005). Among others, they are characterized by the expression on their surface of the chondroitin sulfate proteoglycan (known also as the Neural/glial antigen 2, NG2) and therefore they are also are recognized as NG2-cells (Fig. 1 A, B). Intriguingly, the cells that originated during the first ventral wave during embryogenesis are supposed to be eliminated postnatally, unless there is a need to replace OPCs of the second and the third wave due to alterations in the ongoing gliogenesis, which could be considered as one of the very first mechanisms of tissue regeneration (Kessaris et al., 2006; Naruse et al., 2016). It is worth noting here, that a small population (~ 1-2%) of those glia-committed progenitors seems to retain an internal ability to acquire a neuronal phenotype, as could be deduced from the expression of markers characteristic for emerging neuroblasts (like for instance NF-200 or doublecortin) (Fig. 1 A, B), which might be an important feature in the context of endogenous restorative processes. The newly generated neurons and oligodendrocyte progenitors are particularly vulnerable to insult during the perinatal period, which is a significant challenge for tissue regeneration after the episode of perinatal asphyxia (Janowska et al., 2018).

Emerging oligodendrocyte progenitors almost uniformly populate the brain and spinal cord, either remaining in their undifferentiated state or undergoing a multistage, stepwise process of differentiation, finalized by acquiring the ability to myelinogenesis (Fig. 1 C, D). Enwrapping axons with tight myelin sheaths is the most recognizable function of mature oligodendrocytes. It provide nerve insulation and enables high-fidelity saltatory conduction of signals along axons, ensuring the efficient functioning of the nervous system. However, only part of the heterogeneous OPC population undergoes a differentiation process, while the other one remains scattered in the brain parenchyma, both in the white (8-9% of entire neural cell population) and grey (accounting for 2-3 %) matter (Dawson et al., 2003; Dimou et al., 2008). This almost uniform distribution of OPCs, which are also thought to be the major population of cycling cells within the CNS, is achieved by a specific self-repulsion mechanism (Hughes et al., 2013).

In this way, at the end of the process of developmental gliogenesis, numerous undifferentiated, cycling cells of progenitor characteristics are present within the CNS parenchyma (Fig. 1E). In adulthood, these progenitors serve as precursors of myelin-forming mature oligodendrocytes, but they are also among cells actively reacting to the pathological cues disturbing local tissue homeostasis and supposedly playing a major role in tissue regeneration processes. During lifetime, new neurons (Fig. 1F) and glia can also originate from neurogenic niches, which are located in the subventricular zone (SVZ) adjacent to the lateral ventricles in the brain and the subgranular zone of the hippocampal dentate gyrus (SGZ), between the granule cell layer and the hilus (Doetsch, 2003; Kriegstein and Alvarez-Buylla, 2009; Paul et al., 2017). There are however several lines of evidence that glial precursors generated in adulthood differ in a few essential properties from those originated during development: they exhibit lower proliferation rate and lesser motility but differentiate into mature oligodendrocytes more rapidly and produce myelin sheaths more efficiently (Ruffini et al., 2004; Windrem et al., 2004). Although several studies have reported that the potency to generate neural stem cells declines with age (Lugert et al., 2010; Luo et al., 2006; Lupo et al., 2018; Mosher and Schaffer, 2018), the nervous tissue is a life-long reservoir of precursors, which might replace the cells affected by pathological cues.

3. Role of glia in development and physiological functioning of the central nervous system

Once derived during ontogenesis, glial cells are actively engaged in forming the nervous system, thus becoming indispensable for establishing the neuronal circuit and signal transduction (Clarke and Barres, 2013). They provide structural support and create local tissue microenvironment by secreting biologically active compounds like trophic factors, cytokines and neuromodulators. Astrocytes express axonal guidance molecules, as well as promote synaptogenesis (by secreting synaptogenic molecules like hevin and thrombospondins) and angiogenesis (due to the release of Vascular endothelial growth factor, angiopoietin-1/2, endothelin-1) (Christopherson et al., 2005; Ma et al., 2012; Nakamura-Ishizu et al., 2012). Astrocytic endfeet are involved in forming and maintaining the existence of the blood–brain barrier, covering almost the entire capillary surface (Mathiisen et al., 2010). The physiological functioning of the CNS throughout life-time largely relies also on astrocyte-derived molecules–called gliotransmitters - playing crucial roles in synaptic plasticity and transmission. Accordingly, due to sensing Ca^{2+} fluxes or other processes associated with neuronal activity (reviewed e.g. by Rose et al., 2018; Santello et al., 2012; Schousboe, 2018), astrocytes are able to release neurotransmitters (glutamate, GABA, ATP, glycine, neuropeptide Y) and neuromodulators (like D-serine, taurine, L-aspartate, kynurenic acid) (Blum et al., 2008; Lalo et al., 2014; Verkhratsky et al., 2016). Importantly, those glial cells are also the major suppliers of energy substrates. Glucose, which up-take is facilitated by glucose transporter

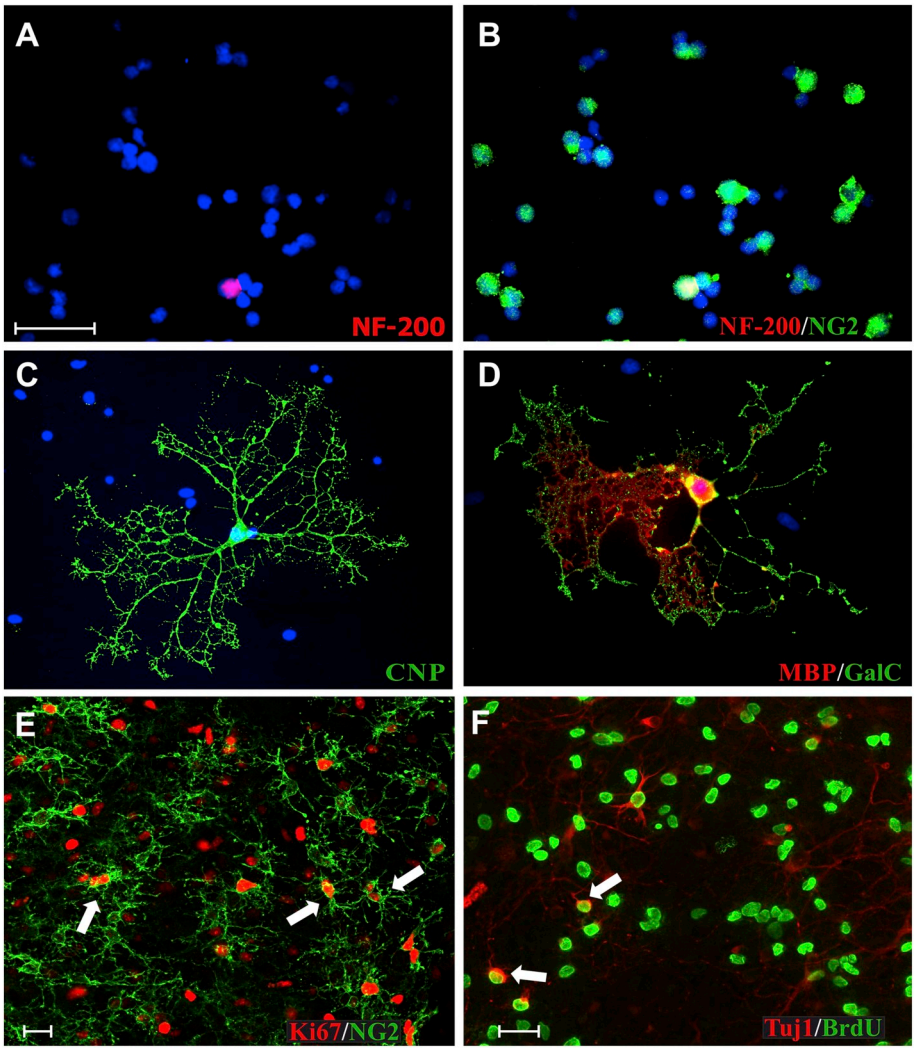

Fig 1. Identifying cell phenotype by immunolabelling with specific antibodies. A, B: Oligodendrocyte progenitor cells (distinguished by the presence of classical NG2 marker, green), isolated from neonatal rat brain, express marker typical for neuroblasts (NF-200, red). C: Differentiating, multibranched oligodendrocyte, expressing 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNP, green); D: Mature oligodendrocyte characterized by the presence of galactocerebroside (GalC, green) and myelin basic protein (MBP, red); E: Dividing glial progenitors (NG2-positive, green), identified by the expression of Ki67 protein (red) in their cell nuclei, present in organotypic hippocampal slices; F: Newly-born (incorporating BrdU, green) progenitors of neuronal cells (TuJ1-positive, red) in organotypic hippocampal slices subjected to ex vivo model of hypoxia-ischemia, indicating endogenous tissue response to the insult by initiating restorative mechanisms. Cell nuclei are labelled with Hoechst 33258 (blue). Scale bar corresponds to 20 μm.

GLUT1, is converted by glycolysis into pyruvate and subsequently to lactate, shuttled via monocarboxylate transporters MCT4 and MCT2 to be used as an energy substrate by neurons.

The energy metabolites ensuring the physiological functioning of neurons are also provided by oligodendrocytes, which are the cells responsible for myelinating the CNS. Covering axons with multilamellar, compact, lipid-rich myelin segments elaborated by individual oligodendroglial processes and separated by nodes of Ranvier, enables their insulation, provides mechanical protection, maintains long-term axonal integrity, as well as allows rapid, saltatory signal transduction. Due to neuron-oligodendrocyte coupling, axons are provided with glucose, pyruvate and lactate, indispensable for their high energy demands (Meyer et al., 2018; Philips and Rothstein, 2017; Zhang et al., 2017b).

In comparison to astrocytes and oligodendrocytes, which are at least of equal number to neurons, microglial cells account for approximately 5–15% of cells inhabiting the CNS (von Bartheld, 2017; Lyck et al., 2009). Although small in number, they are thought to be indispensable for brain development, functioning and defense from the invading pathogens. However the role they play in the nervous tissue is expanded far beyond being the important guardians of the CNS. Mounting evidence suggests that microglial cells are engaged in the process of neurogenesis (Gemma and Bachstetter, 2013; Shigemoto-Mogami et al., 2014; Sierra et al., 2010) and the formation of the nervous tissue by clearing it of apoptotic and malformed cells, the excess of progenitors and synapses, as well as debris and protein aggregates (Cunningham et al., 2013; Mazaheri et al., 2014; Wake et al., 2009). They also promote synaptogenesis, including learning-dependent synapse formation (Kettenmann et al., 2013; Miyamoto et al., 2016; Paolicelli et al., 2011; Parkhurst et al., 2013).

Trophic support conveyed to the neighboring cells and modifying the local tissue microenvironment is the commonest and most significant feature of all types of glial cells. By releasing neurotrophins [NT-3, NT-4, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF)], trophic factors (like glial cell derived neurothropic factor: GDNF), cytokines and interleukins, glial cells guide the CNS development, ensure cellular crosstalk, the proper functioning and self-renewal. By exerting immunomodulatory effects, glia are engaged in promoting physiological regenerative processes (Arcuri et al., 2017; Sung et al., 2014).

4. Response of glial cells to pathophysiological cues

Under pathophysiological conditions or upon injury, resident glial cells are activated and respond to the changed tissue microenvironment in several ways. $NG2^+$ cells which exhibit an inestimable, in the context of tissue regeneration, ability to proliferate throughout the lifespan, serve as a reservoir of glial progenitors for deriving myelinating cells (Simon et al., 2011). They have also been shown to increase their proliferation rate and to initiate migration towards the site of injury (Hesp et al., 2018; Janowska et al., 2018; Tanner et al., 2011; Tripathi and McTigue, 2007). In response to exogenous signals they are able to

modulate their secretory activity, thus releasing protective and neurostimulatory factors (like BDNF, NT-3, IGF-1) (Dai et al., 2003; Du and Dreyfus, 2002; Wilkins et al., 2001, 2003) and a spectrum of cytokines and chemokines (like for instance interleukins IL-1β and IL-17A, chemokines CCL2, CXCL10) (Ettle et al., 2016; Zeis et al., 2016). Among them, the secretion up-regulation of IL-10 is up-regulated in the ex vivo model of neonatal hypoxia-ischemia. In brief, the increase in the extracellular concentration of this anti-inflammatory cytokine in the diseased tissue milieu results in mobilizing of the resident microglial cells, thus exerting an immunomodulatory effect, permissive for subsequent neuroregenerative processes (manifested by the increased neurogenesis and enhanced proliferation of glial progenitors) (Sypecka and Sarnowska, 2014).

Similar effects are observed in astrocytes, another abundant glial cell type. As previously mentioned, the physiologically determined release of plethora of instructive signals by astrocytes orchestrates the development of the nervous system, thus ensuring its proper functioning (Weber and Barros, 2015). In the diseased tissue, their secretory profile has been shown to be changed and potent to modify the local tissue microenvironment, making it either permissive or unsusceptible for the regenerative processes. Many lines of evidence indicate, that astrocytes are able to extracellularly discharge various types of active compounds, acting as part of the neuroglial secretory network (Vardjan and Zorec, 2015). Accordingly, biological molecules are inserted in small vesicles, elaborated to transfer different types of cargo (extensively reviewed by Verkhratsky et al., 2016). Depending mainly on their size and content, a few types of vesicles could be distinguished. The smallest ones, recycling from plasma membranes, are synaptic-like microvesicles carrying glutamate and D-serine (SLMVs, 30–100 nm in diameter and found in groups of 2–15). Dense core vesicles are about 100–600 nm in size, usually deliver peptides, including BDNF and neuropeptide Y, thus being one of the major neuroprotectants and regulators of neurogenesis (Chen et al., 2017; Kowiański et al., 2018; Lai et al., 2018; Reick et al., 2016). Secretory lysosomes are between 300 and 500 nm in size and carry among others ATP and proteolityc enzymes. And finally extracellular vesicles (exosomes and ectosomes) could be distinguished, which are loaded with various bioactive molecules like cytokines, growth factors, signalling proteins, mRNA and microRNA. Owing to such intense paracrine activity, astrocytes are able to contribute to in situ modulating their surrounding tissue milieu and influencing the neighboring cells (Jha et al., 2018; Sung et al., 2014; Zorec et al., 2017).

While considering engagement of glia in regenerative processes initiated after insults, a role of ependymal cells lining the central canal should be taken into account. Ependymal cells, which share many features with neural stem cells, respond to many types of injuries (like for instance trauma, compression or dissection) or pathological signals associated with the ongoing disease by increasing the rate of their proliferation, migrating and differentiating for the purpose of restoring the nervous tissue (Meletis et al., 2008; Moreno-Manzano et al., 2009; Mothe and Tator, 2005). It has been shown that when implanted into the injured site, they can contribute to forming functional neuronal circuits in some experimental models (Sabelström et al., 2014). Mobilizing and directing differentiation of silent ependymal cells seem to be one of the most promising options for regenerative strategies in the case of spinal cord injuries (Panayiotou and Malas, 2013).

In spite the fact that macroglial cells strongly react to pathological conditions affecting the CNS, it is the microglial cells which are the most distinguishable defenders of the brain and the spinal cord from the consequences of the initiated degenerative mechanisms. In their quiescent state, ramified microglia survey the surrounding tissue microenvironment, sensing local milieu with their cell processes. Upon activation in response to pathophysiological stimuli (triggered by injury or invasion of pathogens), they change their morphology, become phagocytic and start to release cytokines and chemokines, helping in combating the neuroinflammatory process with aim of promoting neuroreparative mechanisms (Neumann et al., 2009). The effects exerted by the ongoing secretory activity of cells depend on the phenotype acquired by the patrolling microglia. The pro-inflammatory M1 phenotype, promoted by the exogenous stimulation with for instance interferon gamma (IFNγ), tumor necrosis factor alpha (TNF-α) or interleukine IL-17, leads to expression and release of numerous cytokines such as IL-1α/β, IL-6, IL-12, IL-23, as well as TNF-α or inducible nitric oxide synthases (iNOS. Polarization to M1 phenotype is associated with the onset of neuroinflammation symptoms and-in most cases-progressive tissue damage. And conversely, by acquiring an anti-inflammatory M2 phenotype (supported by for instance glucocorticoids, TGF-β, or interleukins IL-4, IL-10, IL-13), microglia produce different types of molecules like arginase-1 (Arg-1) or insulin-like growth factor 1 (IGF-1), in their effort to overcome neuroinflammation and modulate tissue microenvironment to make it favorable to regenerative processes (Chew et al., 2006; Salvi et al., 2017; Zarruk et al., 2018). It is however worth stressing that microglia polarization is not just a distinction between “unwanted” and “desired” phenotypes, since for instance the enhanced phagocytic activity associated with the M1 state helps to eliminate pathogens or clear the nervous tissue of myelin debris, resulting from leukodystrophic degeneration and containing molecules which exert inhibitory effects on axonal outgrowth and oligodendrocyte maturation.

To summarize, a wide range of bioactive molecules released glial cells in response to pathological conditions is potent to modulate the local microenvironment and exert a significant influence on the neighboring cells. Depending on their secretome composition, this effect might be either detrimental (like enhanced neuroinflammation, delivery of inhibitory molecules, contribution to axon degeneration or cell death and other processes) or beneficial (including elimination of pathogens, delivery of cytokines and chemoattractants triggering physiological reparative mechanisms, like mobilizing progenitors from endogenous reservoirs, guiding their cell-fate and governing their differentiation) (Fig. 2). Moreover, the bioactive compounds are also known to promote glial transdifferentiation, both under physiological and pathophysiological conditions.

5. Exploring the endogenous reservoir of glial cells

The few last decades of intense research on glia functions have considerably enhanced our appreciation of them as active regulators asserting the physiological function of the CNS and potent defenders in pathological conditions. Alterations in their differentiation process, their malfunctioning or depletion due to neurodegenerative mechanisms usually lead to neurological disorders. To prevent the consequences of tissue homeostasis misbalance evoked by pathological cues, neuroreperative mechanisms need to be initiated as quickly as possible. Taking into consideration the abundance of glial progenitors and the heterogeneity of glial cells within the nervous tissue, it seems reasonable to search for potential candidates for cell replacement strategies within the endogenous cell reservoirs.

The idea of using various cell sources for the purpose of regenerating the diseased tissue or organs emerged a few decades ago and evolved later as a result of several approaches, including cell transplantations and the first bioengineering strategies (Lindvall et al., 1988; Perlow et al., 1979). One of the first successful attempts to convert cell fate into alternative phenotypes by means of bioengineering techniques concerned reprogramming mouse embryonic fibroblasts to become myoblasts by treating the cells with 5-azacytidine (an analog of nucleoside cytidine), which is an inhibitor of DNA methyltransferase and acts as an epigenetic modifier (Davis et al., 1987). Another approach, involving transfecting mouse fibroblasts with complementary DNA (cDNA) encoding the mouse MyoD1, was also proved to be effective in converting them into newly generated myoblasts (Tapscott et al., 1988). During the next two decades, the utility of transcription factors and morphogenes in strategies aimed at redirecting and enforcing cell

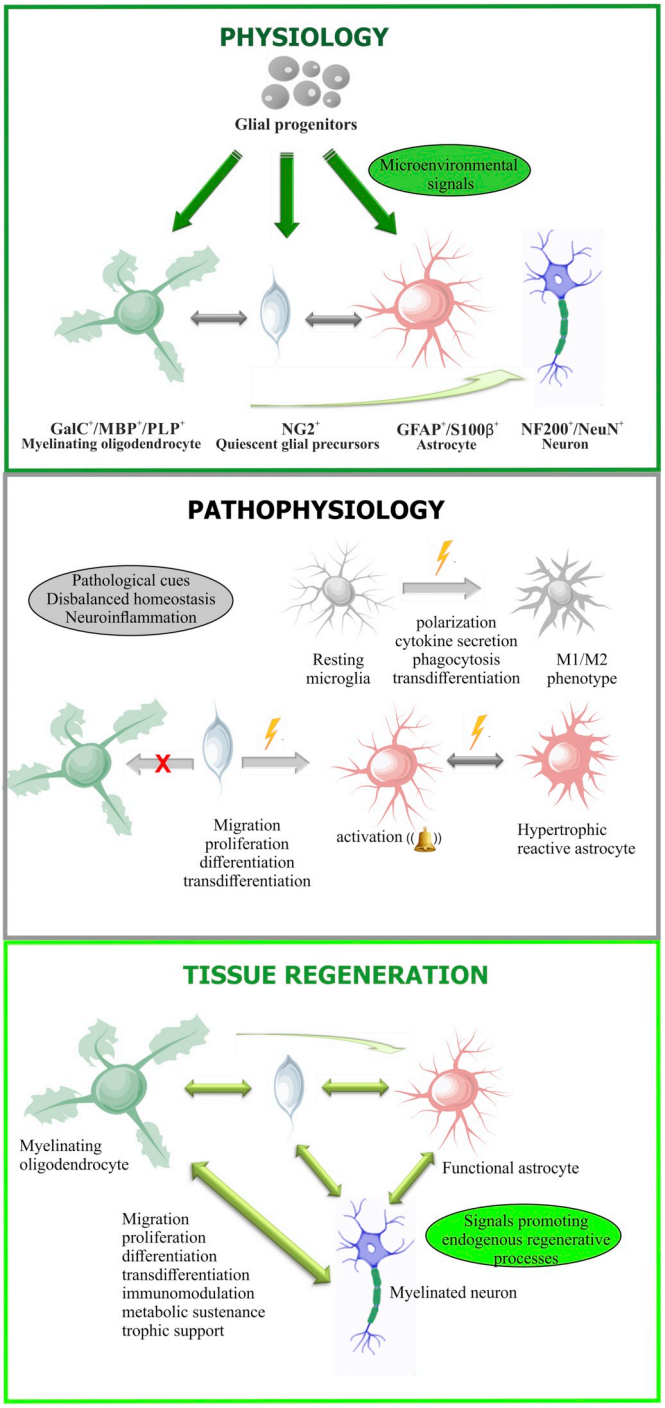

Fig. 2. Glial cells are able to transdifferentiate into alternative phenotypes under both physiological conditions and upon injury, thus exhibiting properties attributed to multipotential neural stem cells. Conversion of cell fate, occurring spontaneously, could be also forced by the application of selected bioactive compounds that are potent to drive cell reprogramming and differentiation.

differentiation was demonstrated in several experiments using embryonic stem cells, as well as in glial cell lineage (Chiba et al., 2003; Heins et al., 2002; Li et al., 2005; Wichterle et al., 2002). However, generating induced pluripotent stem cells (IPSc) by selected transcription factors paved the way for reprogramming cell phenotypes by bioengineering approaches (Takahashi and Yamanaka, 2006), followed by employing strategies aimed at differentiating them into desired phenotypes, including neural functional cells (Tang, 2018; Yang et al., 2017).

To date, applying stem cells encounters serious difficulties, including ethical controversies concerning their sources, immunogenicity, significant heterogeneity within a population derived from even a single source, safety issues and limited effectiveness of their differentiation into required phenotypes (extensively reviewed by Volarevic et al., 2018). Moreover, the immunological system of patients in need of therapy is often largely stimulated due to their having suffered from injury or neurodegenerative disorders. Under such specific circumstances, combining cell therapies with immunosuppressive treatments is quite a challenge. In this context, such treatments may potentially worsen the clinical outcome and heighten the risk of additional side-effects. This disadvantage could be limited to some extent by a personalized medicine approach, for instance by creating in vitro induced pluripotent stem cells (IPSc), derived from the patient's own cells, like for instance skin fibroblasts. Reprogramming somatic cells, most commonly performed by applying so called Yamanaka factors, has been reported to be relatively feasible in the case of induced neural stem cells (iNSCs) (addressed in detail by Shahbazi et al., 2018). As for IPSc however, one can take the multi-step protocols of cell differentiation into consideration, involving the prolonged in vitro cell culturing, often associated with genetic instability due to an accumulation of mutations and the accelerated cell senescence. The risk of tumorigenesis is predominantly associated with the pluripotency state, as well as with the application of selected transcription factors (like c-myc, OCT3/4 or Klf4) intended for cell reprogramming, for they are considered to be potent oncogenic factors, which may contribute to neoplasia (Flynn and Hogarty, 2018; Wang et al., 2018; Wolpaw and Dang, 2018). Purifying the IPSc-derived differentiated cells or applying so called multilineage differentiating stress enduring (Muse) cells, which not until recently came into view and still require further investigation in the context of clinical perspective (Dezawa, 2016; Fisch et al., 2017), are the proposed solutions to overcome some of those disadvantages. The known and verified strategies however are unfortunately both time- and cost-consuming, therefore new solutions are still being looked for.

Taking the above into consideration, exploring the abundant reservoir of endogenous glial cells for transdifferentiation procedures makes it possible to avoid crossing the neural lineage boundaries. In this context, one of the main advantages of targeting glia for neurorestorative strategies is the possibility of limiting the risk of tumorigenesis, for the cells in question are already neurally committed. This approach also allows shortening procedures (which can even be limited to a single step while considering converting cell fate directly). They are less time- and cost-consuming and more effective (depending however on the method used). Strategies aimed at direct differentiating or transdifferentiating glial cells into alternative neural phenotypes have to be preceded however by a wide-range of in vitro studies in order to learn the mechanisms governing cell biology in detail. One of the earliest studies concerning glial cell identity and properties proved that oligodendrocytes and astrocytes could be derived from common, bipotential progenitors, called O-2A cells (Alghamdi and Fern, 2015; Ffrench Constant and Raff, 1986; Levi et al., 1991). Over a decade later, a study on differentiated oligodendrocytes brought a breakthrough result indicating that oligodendroglial cells could be dedifferentiated, acquiring the phenotypic features of neural stem cells (Kondo and Raff, 2004). The ability of glial cells to dedifferentiate or transdifferentiate has been confirmed by numerous in vitro and ex vivo experiments on primary cell cultures, co-cultures and organotypic tissue slices. In some kind of those experiments, the influence of various signals present in either physiological or pathophysiological tissue microenvironment was investigated, e.g. hippocampal vs spinal cord (Leoni et al., 2009; Sypecka et al., 2013; Sypecka and Sarnowska, 2013). Other studies were based on genetic engineering approaches, employing active compounds like transcription factors (Berninger et al., 2007; Chouchane et al., 2017; Corti et al., 2012; Heinrich et al., 2010; Masserdotti et al., 2015), pattering molecules (Cheng et al., 2015; Hu

et al., 2010) and small molecules (Gao et al., 2017; Zhang et al., 2015). Obtaining the above mentioned in vitro results were followed by the in vivo observations that both oligodendroglia and astrocytes could postnatally originate from the same progenitors, both under physiological conditions and after injury (Tatsumi et al., 2018; Tripathi et al., 2010; Zhao et al., 2009; Zhu et al., 2008). Moreover, a very minor population of neonatal glia-committed, NG2-positive cells express neuronal markers too, like NF-200, TuJ1 or DCX (Fig. 1A, B) (Sypecka et al., 2009).

A growing list of evidence suggest that both under physiological, as well as pathophysiological conditions, the $NG2^+$ cells could also give rise in vivo to neurons and astrocytes (Guo et al., 2010; Rivers et al., 2008; Robins et al., 2013; Sypecka et al., 2009; Tsoa et al., 2014). Although astrocytes in the adult brain are thought not to be able to divide under physiological conditions, the activated cells have been shown to acquire some typical markers of neural stem cells and to undergo an intense proliferation process, called reactive gliosis (Buffo et al., 2008). In regard to both the type of insult or disease and the affected CNS region, this process is thought to be beneficial in the context of preventing the diseased tissue from further degeneration and promoting the subsequent regeneration. Accordingly, on one hand reactive astrogliosis, ongoing for instance in the "peri-infarct" area (so called penumbra), adjacent to the region in which the local ischemia occurred, helps to separate the damaged area in the infarct from the surrounding intact tissue, limiting the spread of inflammation and the progress of neurodegeneration (Burda et al., 2016; Magaki et al., 2018; Sims and Yew, 2017). Additionally, the secretory activity of reactive glia might be beneficial in terms of providing cytokines, components of extracellular matrix (like laminin) and growth factors (for instance BDNF, NGF, GDNF, BMP1), thus playing crucial roles in modulating the adaptive responses in neurons, conferring neuroprotection and initiating or enhancing neurogenerative mechanisms (Anderson et al., 2016; Bylicky and Mueller, 2018; Itoh et al., 2018).

On the other hand however, some factors released by active astrocytes for a prolonged time could exacerbate tissue damage. Among them are pro-inflammatory cytokines (e.g. IL-1β, IL-6, TGF-β), which initially help to attract immune cells clearing the nervous tissue from accumulated debris, formed among others by necrotic cells, collapsed microvessels or destroyed myelin lammelae (containing molecules which are regarded as inhibitory factors for axonal outgrowth, like Nogo-A or myelin oligodendrocyte glycoprotein, MOG). Local microenvironment created by chronic neuroinflammation is not conducive however to initiating endogenous restorative mechanism and thus actually hampers tissue regeneration. Other factors known to exert detrimental effects in pathophysiological conditions and to contribute to the ongoing reactive astrogliosis comprise extracellular matrix components, like matrix metalloproteinase-3 (MMP-3), contributing to breaking the blood-brain barrier, as well as molecules inhibiting axonal regeneration and outgrowth, including chondroitin sulfate proteoglycans (CSPGs) and tenascins (several of which have been extensively reviewed elsewhere, e.g. Dyck and Karimi-Abdolrezaee, 2015; Sofroniew, 2014; Quraishe et al., 2018). Those factors are being intensively explored as potential targets for therapeutic interventions, especially in the case of spinal cord injury (Kucher et al., 2018; Nathan and Li, 2017; Sofroniew, 2018). In this context, even if only part of reactive cells could presumably be converted into alternative phenotypes, regenerative processes could be initiated by reestablishing neuron-glia communication, necessary for instance for triggering mechanisms leading to remyelination.

Considering the consequences of astrogliosis mentioned above, it seems to be reasonable to design strategies aimed at targeting reactive glia as step-wise and disease-dependent protocols. Since reactive astrogliosis is nowadays believed to bring about beneficial effects immediately after the injury or the onset of disease (Lukovic et al., 2014), attempts to convert cell fate into alternative neuronal phenotypes should probably be carried out in a later period, when sustained astroglial activity seems to be hampering restorative processes aimed at restoring nervous tissue functions.

From this point of view, intensive proliferation and migration of NG2 progenitors triggered by pathological cues and their subsequent contribution to glial scar formation seems to be a highly undesirable process, especially in the case of spinal cord injury (Hackett and Lee, 2016; Honsa et al., 2016; Okada et al., 2018; Yin et al., 2018). Therefore NG2 cells present in the area of injury are regarded as potential targets for in vivo manipulation to either enhance their differentiation into mature cells ready to remyelinate diseased axons or to enwrap newly generated, extended axons; eventually to be converted into neurons necessary for complete tissue neuroregeneration.

Likewise, the astrocytic transdifferentiation into other neural cell types has been reported as well. The in vivo studies based on injecting a pGfa2eGFP plasmid, which expressed the enhanced green fluorescent protein (eGFP) reporter gene driven by a glial fibrillary acidic protein (GFAP) gene promoter, into the ipsilateral striatum in the animal model of transient middle cerebral artery occlusion (MCAO) allowed to determine that striatal astrocytes transdifferentiate into functional mature neurons following the ischemic brain injury in adult rat brains (Duan et al., 2015; Shen et al., 2016). Another study, performed on the animal model of spinal cord injury, revealed that as much as nearly 10 percent of autologous astrocytes spontaneously transdifferentiate into neurons, expressing the classical neuronal progenitor markers including βIII-tubulin and doublecortin. The process of astrocytic transdifferentiation started as early as 72 h post-lesion and continued for the subsequent few weeks (Noristani et al., 2016). Not until recently it has also been shown, that under certain in vitro conditions, astrocytes can adopt endothelial phenotype. The observed astrocyte-endothelial cell transition could presumably be modulated by miR-194, which is downstream of p53 affecting the expression of genes regulating angiogenesis (Brumm et al., 2017).

Keeping in mind that glia subtypes and neurons are derived from common multipotent neural progenitors and their fate-choice is guided by the influence of extracellular signals present in tissue milieu, the possibility of in vivo pharmacological/genetic modulation of reprogramming processes could be expected, opening new avenues towards a potential use of endogenous glia for neurorestorative strategies.

6. Targeted reprogramming of glial cells into neurons by transcription factors

As alluded above, $NG2^+$ progenitors giving rise to myelinating oligodendrocytes are abundant in the brain and the spinal cord parenchyma, and known to be activated under pathophysiological conditions or upon injury. Since oligodendrocytes undergo a precisely regulated multi-stage process of maturation (Fig. 1 B, C, D), finalized by gaining by the cells the ability to generate myelin components, they could be extremely prone to reprogramming in their the early stages of differentiation (Huang and Dreyfus, 2016; Wheeler and Fuss, 2016). After glial commitment, progenitors express characteristic transcription factors Olig-1 and Olig-2, which are members of the basic helix-loop-helix (bHLH) family determining cell fate. In this context, a question arises if the process could be reversible, resulting in switch to other fate of cells generated from the common neural stem cells. Accordingly, one of the very first experimental trials of in vivo cell reprogramming was based on injecting of retroviral vectors containing a dominant negative form of Olig2 into the lesioned cortex (Table 1) (Buffo et al., 2005). Indeed, it was reported that antagonizing Olig2 function resulted in deriving immature neurons in the lesion area. A similarly constructed retroviral vector, i.e. containing a functionally dominant negative form of Olig2, has been used in the animal model of mild transient brain ischemia (evoked by procedure of the middle cerebral artery occlusion followed by reperfusion). Injection of the vector into the lesioned striatum resulted in generating of functional neurons, as verified by whole-cell patch-clamp recordings in acute brain slices (Kronenberg

Table 1
In vivo reprogramming of glial cells by transcription factors via viral transfection

Type of intervention	Animal model	Outcome of the experiment	Reference
Injection of retroviral vectors containing a dominant negative form of Olig2 into the lesioned cortex 2 days after an injury	Stab wound in the right cerebral neocortex of mouse brain	Generation of immature neurons by antagonizing Olig2 transcription factors in glial progenitor cells	Buffo et al., 2005
Injection of retroviral vectors containing a dominant negative form of Olig2 into into the lateral striatum	Mild transient brain ischemia (middle cerebral artery occlusion)	Resident glial progenitors in the striatum were reprogrammed toward functional neurons (verified by whole-cell patch-clamp recordings of Na^+ currents)	Kronenberg et al., 2010
Retroviral expression of a neural transcription factor, NeuroD1	Stab wound -injured or Alzheimer's disease (AD) model mice	Astrocytes were reprogrammed into glutamatergic neurons, while NG2 cells were reprogrammed into glutamatergic and GABAergic neurons	Guo et al., 2014
Injection of NeuroD1 cloned into adeno-associated virus 9 (AAV9)	Transgenic mice (physiological conditions)	Generation of neurons in the striatum under physiological conditions	Brulet et al., 2017
Lentiviral vector containing eight transcription factors (SOX2, ASCL1, BRN2, KLF4, MYC, MYT1L, OCT4, and ZFP521) and four microRNAs (miR9, miR124, miR125 and miR128) delivered into to target astrocytes in adult mouse striatum	Transgenic mice, aged wild type mice	SOX2 alone is sufficient to reprogram astrocytes into proliferating neuroblast, which after stimulation by BDNF plus noggin or VPA differentiated into neurons	Niu et al., 2013 Niu et al., 2015
retroviral vectors encoding *Ascl1* and *Sox2*	stab wound lesion in the mice cerebral cortex transgenic mice Sox10-iCreER^{T2}/GFP and GLAST^{CreERT2}/GFP	NG2 progenitors converted to immature GABAergic neuron by ectopic expression of Sox2	Heinrich et al., 2014
Lentiviral vector containing Sox2 gene	Spinal cord injury	Conversion of spinal cord -resident astrocytes to neuroblasts, which matured into synapse-forming neurons in vivo	Su et al., 2014 Wang et al., 2016
Ascl1, Lmx1a, Nurr1, inserted into adeno-associated virus (AAV), injected into mouse striatum	NG2-Cre transgenic mice	Conversion of NG2+ progenitors into functional GABAergic neurons	Torper et al., 2015 Pereira et al., 2017
GFAP–adeno-associated virus (AAV) vectors containing Ascl1 injected into the dorsal midbrain, striatum, and cortex	Transgenic mice strains: (*Gad67*)–*GFP* knock-in mice (*GFAP*)–*GFP* mice *Aldh1l1–EGFP* and *Aldh1l1–Cre*	Reprogramming of brain astrocytes into functional neurons	Liu et al., 2015
Injection of retroviral vector containing either Neurog2 alone or with Bcl-2, combined with treatment with antioxidant and ferroptosis inhibitors	stab-wound injury	Conversion of astrocytes into neurons, application of antioxidants facilitated metabolic transition and redox homeostasis	Gascón et al., 2016
recombinant retroviruses expressing Neurog2, Pax6, and Ascl1	Focal cortical ischemia	Neural conversion of non-neuronal cells	Grande et al., 2013

et al., 2010).

Another study focused on testing the effectiveness of a combination of transcription factors including *Ascl1*, *Lmx1a*, and *Nurr1,* inserted into the adeno-associated virus (AAV), on neuronal re-direction of NG2-positive cells. As shown, this approach resulted in converting the cell in question into the functional GABAergic neurons (Pereira et al., 2017; Torper et al., 2015).

Astrocytes are the major subpopulation of glial cells within the nervous system, therefore they have been the target of many studies aimed at redirecting cell fate. Likewise, it has been reported that the neural transcription factor NeuroD1 is another pattering molecule potent in reversing glial cell differentiation and instructing them to become neurons. Tested in stab wound injured or Alzheimer's disease (AD) mice models, it has turned out to be efficient in reprogramming astrocytes into glutamatergic neurons, while the NG2 cells were reprogrammed into glutamatergic and GABAergic neurons (Guo et al., 2014). Recently, this factor has also been tested on non-reactive astrocytes and has been shown to promote their transdifferentiation into neurons in the striatum, but not the cortex, proving however that switching between glia-neuron phenotypes is possible under physiological conditions (Brulet et al., 2017). Another study focused on verifying the reprogramming efficiency of several microRNAs (miR9, miR124, miR125 and miR128), as well as genes encoding the selected transcription factors (ASCL1, BRN2, KLF4, MYC, MYT1L, OCT4, SOX2 and ZFP521) (Niu et al., 2013, 2015). Interestingly, transcription factor Sox2 alone has been shown to be sufficient to reprogram astrocytes residing in mice striatum into proliferative neuroblasts. By providing neurotrophic stimulation due to BDNF administration combined with noggin or valproic acid (VPA, histone deacetylase inhibitor) supplementation, the newly-born neuroblast differentiated into neurons. This observation has been also confirmed by studies aimed at redirecting the astrocytic fate into a neuronal phenotype by injecting a lentiviral vector containing the Sox2 gene into the injured spinal cord (Su et al., 2014; Wang et al., 2016).

7. Directed glial differentiation and modulation of their activity

Reprogramming strategies based on viral vector injection are associated however with the necessity of a precise neurosurgery and the introduction of non-human genetic material, which is thought to be controversial in the context of clinical usage (Biasco et al., 2012). Recognizing those limitations, alternative therapies aimed at complex regeneration of the neural tissue are being searched for by testing out various approaches (Table 2). One of the promising strategies is

Table 2
Enhancing tissue regeneration by genetic manipulation and pharmacological interventions targeted to neural cells

Bioactive compound	Potential effect on neural cells and processes	Reference
Transcription factors (e.g. Olig2, Sox2, Ascl1, Lmx1a, Nurr1, KLF4, MYC, MYT1L, OCT4, and ZFP521, Neurog2)	Direct and relatively highly efficient cell reprogramming and transdifferentiation	Buffo et al., 2005; Kronenberg et al., 2010; Guo et al., 2014; Torper et al., 2015; Brulet et al., 2017; Pereira et al., 2017
Morphogenes (Shh, BMP, TGFβ, retinoic acid)	Driving cell dedifferentiation and commitment	Buzanska et al., 2009; Yan et al., 2013; Espinosa-Jeffrey et al., 2016; Khazaei et al., 2017
Small molecules (e.g. valproic acid, sodium butyrate, purmorphamine forskolin, repsox, benztropine, clemastine)	Effective in conversion of cell fate by epigenetic regulation (applied as a cocktail of bioactive molecules), promoting microglial polarization into anti-inflammatory M2 phenotype, enhancing cell maturation and remyelination	Su et al., 2014; Cheng et al., 2015; Zhang et al., 2015; Wang et al., 2016; Gao et al., 2017
microRNAs (e.g. miR-302/367; miRs-146a, miR-124-3p)	Effective modulators of cell fate switch and microglial polarization	Ponomarev et al., 2013;; Ghasemi-Kasman et al., 2017; Liu et al., 2017; Saika et al., 2017; Huang et al., 2018; Mo et al., 2018
Trophic factors administration (BDNF, GDNF, CNTF, T3, PDGF-AA, IGF-1, T3)	Boosting neurogenesis or gliogenesis, governing cell differentiation	Heinrich et al., 2010; Cheng et al., 2015; Niu et al., 2015; Sypecka et al., 2017
Purified exosomes and small vesicles derived from neural and stem cells	Carriers of natural, cell derived biomolecules (microRNAs, cytokines, trophic factors) thus modulating local microenvironment and cell functioning	Doeppner et al., 2015; Xin et al., 2017; Drommelschmidt et al., 2017; Ophelders et al., 2016; Ruppert et al., 2018

modifying glial cell activity in vivo. As mentioned above, glial cells are highly sensitive to pathological cues and respond by adjusting their biological functions to the changed in situ conditions. Likewise, they can enhance their proliferation, initiate migration triggered by chemoattractants, change their morphology (e.g. become phagocytic in the case of microglia), modulate their secreting activity and even spontaneously transdifferentiate in vivo. Unfortunately, one of the side-effects of glial activation (in terms of regenerative processes) is also a local delivery of inhibitory molecules, which alters axon outgrowth and hampers endogenous restoring mechanisms. To overcome the local tissue crisis, the modulation of local tissue microenvironment (Chew and DeBoy, 2015; Grande et al., 2013) and promotion of desired type of glial activity might be enforced, by for instance pharmacological treatment with various sorts of active compounds.

Accordingly, since the first line of neural tissue self-defense is activation of resident microglia, which could exert either pro- or anti-inflammatory effects depending on their secretory profile, modulating their polarization into a desired phenotype seems to be one of the most obvious targets for potential pharmacological intervention. To date, there are several lines of evidence that so called small molecules are potent modulators of microglial activity. Those bioactive molecules, usually of low molecular weight (< 900 daltons) and a diameter of about 1 nm, may act as inhibitors of nuclear receptors (like pioglitazone, DSP-865 or SNU-BP, being the PPARγ agonist and promoting the M1 to M2 switch or an enhanced microglial phagocytosis), modulators of metabolism-associated molecules (for instance metformin activating AMPK or fidarestat serving as an inhibitor of aldose reductase), inhibitors of histone deacetylases (helpful in epigenetic regulation of the acquired phenotype) or regulators for redox signaling molecules (e.g. NOX) (Song and Suk, 2017; Tang and Le, 2016). Different types of small molecules are also potent regulators of oligodendroglial lineage, including glial-commitment and the enhancement of myelinating potential (Azim et al., 2017; Medina-Rodríguez et al., 2017; Peppard et al., 2015). Among them, epigenetic and transcriptional regulators can be found, like valproic acid or sodium butyrate (Liu et al., 2012; Ziemka-Nalecz et al., 2017). Pharmacological treatment based on small molecules seems to be attractive in the context of their wide selection, effective tissue and cell permeability, multiple possible ways of administration and the encouraging results of the already published preclinical studies. Due to a wide range of easily available small molecules and their different effects on various cell types, strategies designed to as sequential administration of the selected compounds (or their combination) could be a solution for achieving complex tissue regeneration. Likewise, it has been shown that a combination of small molecules alone is sufficient to induce cell conversion into alternative phenotypes, without reintroducing exogenous genes (Cheng et al., 2015; Liu et al., 2015). One of the very recent study reports that achemical cocktail composed of small molecules (VPA, Chir99021, Repsox, forskolin, BET151 and ISX-9), trophic factors (BDNF, GDNF, IGF) and metabolic molecules (ascorbic acid, dibutyryl-cAMP) efficiently promoted direct generation of human neuronal cells from adult astrocytes (Gao et al., 2017). What could bring optimal solutions for regenerative medicine in the foreseeable future is intensifying the in vitro and in vivo pre-clinical studies aimed at testing the safety of chemical cocktails for all the cells constituting the damaged tissue, establishing pharmacokinetics and pharmacodynamics of particular compounds and verifying the potential side effects in all aspects of undesirable or unexpected reactions.

Another promising approach in the context of directing cell reprogramming in vivo is based on applying selected microRNAs (miRs), with their confirmed capability of governing cell differentiation or/and secretory activity. Those small regulatory RNAs are known to be involved in posttranslational gene regulation. The strategy utilizes two opposite modes of intervention. While the first one involves administrating exogenous miRNAs to promote the switch of cell fate, followed by governed differentiation into functional specialized cells and subsequent tissue repair, the other one is aimed at antagonizing specific miRNAs that inhibit either cell conversion or/and differentiation into phenotypes needed for regenerative processes. Recently, the former procedure has been effectively used to convert human astrocytes into neuroblasts both in vivo and in vitro by administrating miR-302/367 in the form of viral particles, although an analogous procedure applied to adult mouse astrocytes required a combination of miRs with valproic acid (VPA) (Ghasemi-Kasman et al., 2015). Functional assays of miR-302/367-induced neurons indicate that newly generated cells fire repetitive action potentials and contribute to reducing the behavioral impairment in the experimental model of Alzheimer's disease (Ghasemi-Kasman et al., 2018). Analogously, miR-302/367 used together with VPA have been proven to be able to redirect the astrocytic phenotype into oligodendrocyte progenitor cells and even into myelinating cells in the cuprizone-induced model of demyelination (Ghasemi-Kasman et al., 2017). In turn, a procedure involving the latter type of approach based on blocking miR-365, has enhanced the PAX6-mediated astrocytic fate-

conversion into neurons after ischemic stroke (Mo et al., 2018).

Enhancement of oligodendrocyte commitment and differentiation might be also modulated by potential usage of miRs, specific for this type of glial cells and often disregulated under pathological conditions (Cunha et al., 2017; Galloway and Moore, 2016; McCoy, 2017; Xiao et al., 2018). Accordingly, experimental trials with the overexpression of miRs-146a have been shown to promote oligodendrogenesis in the stroke model (Liu et al., 2017) and remyelination in the cuprizone model of demyelinating injury (Zhang et al., 2017a). Similarly, specific microRNAs have been identified to govern the fate and functioning of microglia (Ponomarev et al., 2013; Saika et al., 2017). Applying microRNAs for therapeutic purposes successfully, safely and efficiently is still however a significant challenge. The small RNA fragments have to be inserted in a stable carrier able to pass effectively through the blood-brain barrier and to be protected from the in vivo degradation. Next, they need to navigate properly to reach the targeted cells and efficiently affect their functions, without causing side-effects. The currently tested carriers include cationic liposomes, cationic lipid nanoparticles, gold nanoparticles, hydrogels, polyethylenimines nanoplexes, mesoporous silica nanoparticles and many others (reviewed by Wen, 2016).

Interesting observations emerged while analyzing the content of exosomes derived from different types of neural cells, both under physiological and pathological conditions. The results contribute to the growing understanding of the role exosomes play in cellular interactions. They have been shown to contain different miRs governing cell functions and to modulate their response to pathological cues (Jovičić and Gitler, 2017; Kurachi et al., 2016; Yu et al., 2016). For instance, one of the recent studies has shown that miR-124-3p promoted the polarization of microglia to an anti-inflammatory M2 phenotype and the microglial exosomes containing miR-124-3p efficiently inhibited neuronal inflammation and contributed to neurite outgrowth via their transfer into neurons in the model of traumatic brain injury (Huang et al., 2018).

Exosomes, which are secreted by the majority of cells and are present both in extracellular compartments as well as in physiological fluids (like for instance blood, saliva, cerebrospinal and amniotic fluids, breast milk), have been identified as carriers of bioactive molecules and therefore have gained a significant interest as a potential therapeutic means for tissue repair. Special attention is paid to exosomes released by stem cells, which are well recognized in terms of exerting beneficiary trophic, anti-apoptotic, angiogenic and anti-inflammatory effects (Dabrowska et al., 2017; Koniusz et al., 2016). This support, which is significantly relevant to triggering endogenous neuroreparative mechanisms, is conveyed to the neighboring cells in a paracrine manner due to a release of a plethora of growth factors, as well as chemokines and cytokines. A growing list of evidence suggests that the effects attributed to cell therapies based on stem cell transplantation might be achieved-at least to some extent-by administrating a purified exosome fraction. Not until recent years, mesenchymal stem cell-derived exosomes have proved themselves to be efficient in promoting neural plasticity, improving neuroregeneration and preventing postischemic immunosuppression in the animal models of stroke (Doeppner et al., 2015; Xin et al., 2013, 2017), traumatic brain injury (Zhang et al., 2017c), perinatal asphyxia (Drommelschmidt et al., 2017; Ophelders et al., 2016), cytotoxicity of amyloid-β oligomers (de Godoy et al., 2018) and spinal cord injury (Ruppert et al., 2018). The satisfying results obtained with therapies using purified cell-derived exosomes obtained in many laboratories worldwide are also promising for future application in targeted cellular reprogramming for the purpose of neural tissue regeneration.

8. Advantages and disadvantages of the transdifferentiation strategies

As previously mentioned, targeting glia for transdifferentiation strategies makes it possible to avoid crossing the neural lineage boundaries, which is the main advantage of this approach. This allows limiting the risk of tumorigenesis and usually shortens procedures, for there is no need to pass through several stages of the differentiation process (including pluripotency state), as glial cells are already neurally committed. The disadvantages of redirecting cell fate into alternative neural phenotypes are predominantly associated with the applied techniques. First of all, the in vitro versus in vivo approach should be considered.

Accordingly, when propagating cells in vitro with the aim of obtaining sufficient biological material for cell transplantation strategies, even in restricted and well defined culture conditions they might be primed by media components (Jung et al., 2012; Teixeira et al., 2015), which increases the possibility of triggering immunological response. Moreover, cellular composition and cell phenotypes differ depending on the CNS region, in which the specialized areas are distinguished. Therefore the local milieu of extracellular factors present in tissue microenvironment, as well as signals derived from the neighboring cells might exert a direct influence on the terminal cell identity. In this context, the in vivo approach seems to be a reasonable solution, strongly depending however on the technique chosen to switch cell fate.

For instance, introducing viral particles encoding transcription factors, which have been reported to be efficient inducers of trandifferentiation, is associated with triggering the risk of insertional mutagenesis, causing genomic instability and activating undesired gene expression, thus increasing the possibility of differentiating cells into unwanted phenotypes or initiating process of tumorigenesis. This risk could be partially minimalized by using non-integrative virus carriers (for instance adenoviruses like Sedai virus instead of retroviruses). In this context, the emerging technique based on applying the microRNAs seems to be both promising and effective. The main obstacle seems to be the relatively low endogenous stability of miRNAs, requiring several repetitive applications (thus generating additional costs).

On the contrary, another approach based on administrating small molecules is relatively cheap and offer a wide-range of chemical compounds. Combining selected factors (acting at the transcriptional, epigenetic or metabolic levels) might be considered as one of the most effective techniques in redirecting cell fate and governing differentiation processes. The main difficulty for small molecules when applied in vivo, is to reach and enter the targeted cells.

Significant disadvantages of this strategy are also the supposed genotoxicity and cytotoxicity of many of those potent chemical compounds. However, since small molecules are considered to be future pharmacotherapeutics, they have to undergo strict procedures dedicated to drug development, in which the potential cytotoxic effect is verified before clinical usage.

Considering the advantages and disadvantages of various strategies aimed at converting cell fate safely and efficiently, a lesson can be learnt from the recently obtained results of stem cell transplantations. Although replacing depleted cells directly by transplanting grafts seemed to be ineffective in many pre-clinical trials, the so called bystander mechanisms are thought to have significantly contributed to tissue regeneration processes. These effects are conveyed by multiple factors (Pires et al., 2016; Salgado et al., 2015; Zheng et al., 2018), also those encapsulated in the extracellular vesicles derived from the transplanted cells. The safety and effectiveness-related questions concern the content of vesicles and their endogenous stability, nonetheless their usage seems to be one of the most promising strategies in the context of future clinical therapies.

Taking the advantages, possible limitations and efficiency of the reported approaches into account, it seems that a combination of the above discussed techniques, as well as newly designed strategies of co-transplantation of cells derived from various sources (e.g. ependymal cells, Müller glia) should be considered and verified in the in vitro and the in vivo pre-clinical studies (Alastrue-Agudo et al., 2018; Jorstad et al., 2017; Rivetti di Val Cervo et al., 2017; Xia and Ahmad, 2016).

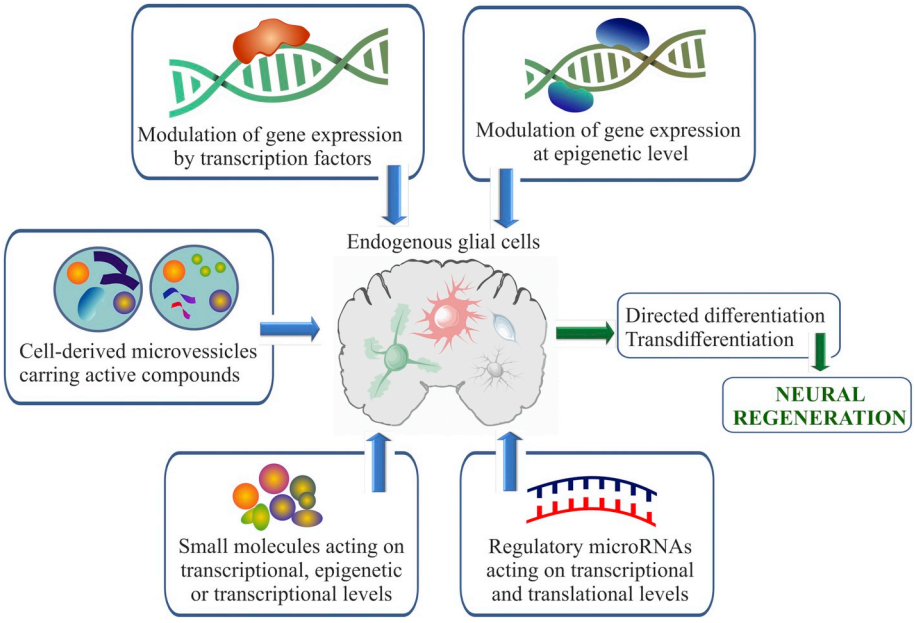

Fig. 3. Strategies for glial cell transdifferentiation, based on different bioengineering approaches.

9. Conclusions

Glial cells, which orchestrate the central nervous system development and ensure its proper physiological functioning, are proven to be highly sensitive to the harmful influence of pathological cues and tissue misbalance, as well as to the modulation of their commitment, differentiation and even the fate-switch by different types of bioactive molecules. The compounds that are potent in guiding in vivo cell fate conversion and driving cell differentiation, include transcription factors, microRNAs, small molecules, morphogens and trophic factors, which are helpful in boosting the enforced neuro-or gliogenesis and the subsequent cell maturation into desired phenotypes (Fig. 3). Optimal strategies for each type of disease, in which a complex tissue regeneration is needed, are still being searched for and are to be designed basing on their proven safety and effectiveness. There is a general consensus that eliminating potential side-effects is the highest priority when clinical application is considered. Other main criteria include the stability of a chosen compound under in vivo conditions, the feasibility of administration, the efficiency in reaching and reprogramming target cells and the lasting beneficial effects. The hope-rising results of preclinical studies together with the existence of a wide-ranged and abundant reservoir of endogenous glial cells, which are responsive to external stimulation, open up new opportunities in terms of developing new approach and beginning new experimental trials. However, taking into consideration a large number of neurological diseases to be cured, in which the damaged nervous tissue needs to be regenerated, research studies aimed at endogenous glia reprogramming need to be intensified to foster clinical treatment application.

Declaration of conflicting interest

The authors declare that they have no conflict of interest.

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References

Alastrue-Agudo, A., Rodriguez-Jimenez, F.J., Mocholi, E.L., De Giorgio, F., Erceg, S., Moreno-Manzano, V., 2018. FM19G11 and Ependymal Progenitor/Stem Cell Combinatory Treatment Enhances Neuronal Preservation and Oligodendrogenesis after Severe Spinal Cord Injury. Int. J. Mol. Sci. 19 (1) (pii: E200).

Alghamdi, B., Fern, R., 2015. Phenotype overlap in glial cell populations: astroglia, oligodendroglia and NG-2(+) cells. Front. Neuroanat. 9, 49.

Anderson, M.A., Burda, J.E., Ren, Y., Ao, Y., O'Shea, T.M., Kawaguchi, R., Coppola, G., Khakh, B.S., Deming, T.J., Sofroniew, M.V., 2016. Astrocyte scar formation aids central nervous system axon regeneration. Nature 532 (7598), 195–200.

Arcuri, C., Mecca, C., Bianchi, R., Giambanco, I., Donato, R., 2017. The Pathophysiological Role of Microglia in Dynamic Surveillance, Phagocytosis and Structural Remodeling of the Developing CNS. Front. Mol. Neurosci. 10, 191.

Azim, K., Angonin, D., Marcy, G., Pieropan, F., Rivera, A., Donega, V., Cantù, C., Williams, G., Berninger, B., Butt, A.M., Raineteau, O., 2017. Pharmacogenomic identification of small molecules for lineage specific manipulation of subventricular zone germinal activity. PLoS Biol. 15 (3), e2000698.

Bahney, J., von Bartheld, C.S., 2018. The Cellular Composition and Glia-Neuron Ratio in the Spinal Cord of a Human and a Nonhuman Primate: Comparison With Other Species and Brain Regions. Anat. Rec. (Hoboken) 301, 697–710.

von Bartheld, C.S., 2017. Myths and truths about the cellular composition of the human brain: A review of influential concepts. J. Chem. Neuroanat. pii: S0891-0618(17)30060-1.

Berninger, B., Costa, M.R., Koch, U., Schroeder, T., Sutor, B., Grothe, B., Götz, M., 2007. Functional properties of neurons derived from in vitro reprogrammed postnatal astroglia. J. Neurosci. 27 (32), 8654–8664.

Biasco, L., Baricordi, C., Aiuti, A., 2012. Retroviral integrations in gene therapy trials. Mol. Ther. 20 (4), 709–716.

Blum, A.E., Joseph, S.M., Przybylski, R.J., Dubyak, G.R., 2008. Rho-family GTPases modulate Ca(2+)-dependent ATP release from astrocytes. Am. J. Phys. Cell Phys. 295, C231–C241.

Brulet, R., Matsuda, T., Zhang, L., Miranda, C., Giacca, M., Kaspar, B.K., Nakashima, K., Hsieh, J., 2017. NEUROD1 Instructs Neuronal Conversion in Non-Reactive Astrocytes. Stem Cell Reports 8 (6), 1506–1515.

Brumm, A.J., Nunez, S., Doroudchi, M.M., Kawaguchi, R., Duan., J, Pellegrini, M., Lam, L., Carmichael, S.T., Deb, A., Hinman, J.D., 2017. Astrocytes Can Adopt Endothelial Cell Fates in a p53-Dependent Manner. Mol. Neurobiol. 54(6), 4584-4596.

Buffo, A., Vosko, M.R., Ertürk, D., Hamann, G.F., Jucker, M., Rowitch, D., Götz, M., 2005. Expression pattern of the transcription factor Olig2 in response to brain injuries: implications for neuronal repair. Proc. Natl. Acad. Sci. U. S. A. 102 (50), 18183–18188.

Buffo, A., Rite, I., Tripathi, P., Lepier, A., Colak, D., Horn, A.P., Mori, T., Götz, M., 2008. Origin and progeny of reactive gliosis: A source of multipotent cells in the injured brain. Proc. Natl. Acad. Sci. U. S. A. 105 (9), 3581–3586.

Burda, J.E., Bernstein, A.M., Sofroniew, M.V., 2016. Astrocyte roles in traumatic brain injury. Exp. Neurol. 275, 305–315.

Buzanska, L., Sypecka, J., Nerini-Molteni, S., Compagnoni, A., Hogberg, H.T., del Torchio, R., Domanska-Janik, K., Zimmer, J., Coecke, S., 2009. A human stem cell-based model for identifying adverse effects of organic and inorganic chemicals on the developing nervous system. Stem Cells 27 (10), 2591–2601.

Bylicky, M.A., Mueller, G.P., Day., R.M., 2018. Mechanisms of Endogenous Neuroprotective Effects of Astrocytes in Brain Injury. Oxidative Med. Cell. Longev. 2018:6501031. doi: https://doi.org/10.1155/2018/6501031.

Chen, S.D., Wu, C.L., Hwang, W.C., Yang, D.I., 2017. More Insight into BDNF against Neurodegeneration: Anti-Apoptosis, Anti-Oxidation, and Suppression of Autophagy.

Int. J. Mol. Sci. 18 (3) (pii: E545).
Cheng, L., Gao, L., Guan, W., Mao, J., Hu, W., Qiu, B., Zhao, J., Yu, Y., Pei, G., 2015. Direct conversion of astrocytes into neuronal cells by drug cocktail. Cell Res. 25 (11), 1269–1272.
Chew, L.J., DeBoy, C.A., 2015. Pharmacological approaches to intervention in hypomyelinating and demyelinating white matter pathology. Neuropharmacology 110 (Pt B), 605–625.
Chew, L.J., Takanohashi, A., Bell, M., 2006. Microglia and inflammation: impact on developmental brain injuries. Ment. Retard. Dev. Disabil. Res. Rev. 12 (2), 105–112.
Chiba, S., Iwasaki, Y., Sekino, H., Suzuki, N., 2003. Transplantation of motoneuron-enriched neural cells derived from mouse embryonic stem cells improves motor function of hemiplegic mice. Cell Transplant. 2 (5), 457–468.
Chouchane, M., Melo de Farias, A.R., Moura, D.M.S., Hilscher, M.M., Schroeder, T., Leão, R.N., Costa, M.R., 2017. Lineage Reprogramming of Astroglial Cells from Different Origins into Distinct Neuronal Subtypes. Stem Cell Reports 9 (1), 162–176.
Christopherson, K.S., Ullian, E.M., Stokes, C.C., Mullowney, C.E., Hell, J.W., Agah, A., Lawler, J., Mosher, D.F., Bornstein, P., Barres, B.A., 2005. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell 120, 421–433.
Clarke, L.E., Barres, B.A., 2013. Emerging roles of astrocytes in neural circuit development. Nat. Rev. Neurosci. 14 (5), 311–321.
Corti, S., Nizzardo, M., Simone, C., Falcone, M., Donadoni, C., Salani, S., Rizzo, F., Nardini, M., Riboldi, G., Magri, F., Zanetta, C., Faravelli, I., Bresolin, N., Comi, G.P., 2012. Direct reprogramming of human astrocytes into neural stem cells and neurons. Exp. Cell Res. 318 (13), 1528–1541.
Cunha, C., Santos, C., Gomes, C., Fernandes, A., Correia, A.M., Sebastião, A.M., Vaz, A.R., Brites, D., 2017. Downregulated Glia Interplay and Increased miRNA-155 as Promising Markers to Track ALS at an Early Stage. Mol. Neurobiol. https://doi.org/10.1007/s12035-017-0631-2. (2017 Jun 13).
Cunningham, C.L., Martínez-Cerdeño, V., Noctor, S.C., 2013. Microglia regulate the number of neural precursor cells in the developing cerebral cortex. J. Neurosci. 33 (10), 4216–4233.
Dabrowska, S., Sypecka, J., Jablonska, A., Strojek, L., Wielgos, M., Domanska-Janik, K., Sarnowska, A., 2017. Neuroprotective Potential and Paracrine Activity of Stromal Vs. Culture-Expanded hMSC Derived from Wharton Jelly under Co-Cultured with Hippocampal Organotypic Slices. Mol. Neurobiol. https://doi.org/10.1007/s12035-017-0802-1. (2017 Nov 13).
Dai, X., Lercher, L.D., Clinton, P.M., Du, Y., Livingston, D.L., Vieira, C., Yang, L., Shen, M.M., Dreyfus, C.F., 2003. The trophic role of oligodendrocytes in the basal forebrain. J. Neurosci. 23 (13), 5846–5853.
Davis, R.L., Weintraub, H., Lassar, A.B., 1987. Expression of a single transfected cDNA converts fibroblasts to myoblasts. Cell 51 (6), 987–1000.
Dawson, M.R., Polito, A., Levine, J.M., Reynolds, R., 2003. NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol. Cell. Neurosci. 24 (2), 476–488.
de Godoy, M.A., Saraiva, L.M., de Carvalho, L.R.P., Vasconcelos-Dos-Santos, A., Beiral, H.J.V., Ramos, A.B., Silva, L.R.P., Leal, R.B., Monteiro, V.H.S., Braga, C.V., de Araujo-Silva, C.A., Sinis, L.C., Bodart-Santos, V., Kasai-Brunswick, T.H., Alcantara, C.L., Lima, A.P.C.A., da Cunha-E Silva, N.L., Galina, A., Vieyra, A., De Felice, F.G., Mendez-Otero, R., Ferreira, S.T., 2018. Mesenchymal stem cells and cell-derived extracellular vesicles protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers. J. Biol. Chem. 293 (6), 1957–1975.
Dezawa, M., 2016. Muse Cells Provide the Pluripotency of Mesenchymal Stem Cells: Direct Contribution of Muse Cells to Tissue Regeneration. Cell Transplant. 25 (5), 849–861.
Dimou, L., Simon, C., Kirchhoff, F., Takebayashi, H., Gotz, M., 2008. Progeny of Olig2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. J. Neurosci. 28(41), 10434–10442.
Diniz, L.P., Almeida, J.C., Tortelli, V., Vargas Lopes, C., Setti-Perdigão, P., Stipursky, J., Kahn, S.A., Romão, L.F., de Miranda, J., Alves-Leon, S.V., de Souza, J.M., Castro, N. G., Panizzutti, R., Gomes, F.C., 2012. Astrocyte-induced synaptogenesis is mediated by transforming growth factor β signaling through modulation of D-serine levels in cerebral cortex neurons. J. Biol. Chem. 287(49), 41432-41445.
Doeppner, T.R., Herz, J., Gorgens, A., Schlechter, J., Ludwig, A.K., Radtke, S., de Miroschedji, K., Horn, P.A., Giebel, B., Hermann, D.M., 2015. Extracellular vesicles improve post-stroke neuroregeneration and prevent postischemic immunosuppression. Stem Cells Transl. Med. 4, 1131–1143.
Doetsch, F., 2003. A niche for adult neural stem cells. Curr. Opin. Genet. Dev. 13 (5), 543–550.
Drommelschmidt, K., Serdar, M., Bendix, I., Herz, J., Bertling, F., Prager, S., Keller, M., Ludwig, A.K., Duhan, V., Radtke, S., 2017. Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury. Brain Behav. Immun. 60, 220–232.
Du, Y., Dreyfus, C.F., 2002. Oligodendrocytes as providers of growth factors. J. Neurosci. Res. 68 (6), 647–654.
Duan, C.L., Liu, C.W., Shen, S.W., Yu, Z., Mo, J.L., Chen, X.H., Sun, F.Y., 2015. Striatal astrocytes transdifferentiate into functional mature neurons following ischemic brain injury. Glia 63 (9), 1660–1670.
Dyck, S.M., Karimi-Abdolrezaee, S., 2015. Chondroitin sulfate proteoglycans: Key modulators in the developing and pathologic central nervous system. Exp. Neurol. 269, 169–187.
Espinosa-Jeffrey, A., Blanchi, B., Biancotti, J.C., Kumar, S., Hirose, M., Mandefro, B., Talavera-Adame, D., Benvenisty, N., de Vellis, J., 2016. Efficient Generation of Viral and Integration-Free Human Induced Pluripotent Stem Cell-Derived Oligodendrocytes. Curr Protoc Stem Cell Biol. 17 (38) (2D.18.1-2D.18.27).
Ettle, B., Schlachetzki, J.C.M., Winkler, J., 2016. Oligodendroglia and Myelin in Neurodegenerative Diseases: More Than Just Bystanders? Mol. Neurobiol. 53 (5), 3046–3062.
Ffrench Constant, C., Raff, M.C., 1986. The oligodendrocyte-type-2 astrocyte cell lineage is specialized for myelination. Nature 323 (6086), 335–338.
Fisch, S.C., Gimeno, M.L., Phan, J.D., Simerman, A.A., Dumesic, D.A., Perone, M.J., Chazenbalk, G.D., 2017. Pluripotent nontumorigenic multilineage differentiating stress enduring cells (Muse cells): a seven-year retrospective. Stem Cell Res Ther 8 (1), 227.
Flynn, A.T., Hogarty, M.D., 2018. Myc, Oncogenic Protein Translation, and the Role of Polyamines. Med Sci (Basel). 6 (2) (pii: E41).
Fuccillo, M., Joyner, A.L., Fishell, G., 2006. Morphogen to mitogen: the multiple roles of hedgehog signalling in vertebrate neural development. Nat. Rev. Neurosci. 7, 772–783.
Galloway, D.A., Moore, C.S., 2016. miRNAs As Emerging Regulators of Oligodendrocyte Development and Differentiation. Front. Cell. Dev. Biol. 4, 59.
Gao, L., Guan, W., Wang, M., Wang, H., Yu, J., Liu, Q., Qiu, B., Yu, Y., Ping, Y., Bian, X., Shen, L., Pei, G., 2017. Direct Generation of Human Neuronal Cells from Adult Astrocytes by Small Molecules. Stem Cell Reports 8 (3), 538–547.
García-Cabezas, M.Á., John, Y.J., Barbas, H., Zikopoulos, B., 2016. Distinction of Neurons, Glia and Endothelial Cells in the Cerebral Cortex: An Algorithm Based on Cytological Features. Front. Neuroanat. 10, 107.
Gascón, S., Murenu, E., Masserdotti, G., Ortega, F., Russo, G.L., Petrik, D., Deshpande, A., Heinrich, C., Karow, M., Robertson, S.P., Schroeder, T., Beckers, J., Irmler, M., Berndt, C., Angeli, J.P., Conrad, M., Berninger, B., Götz, M., 2016. Identification and Successful Negotiation of a Metabolic Checkpoint in Direct Neuronal Reprogramming. Cell Stem Cell 18 (3), 396–409.
Gemma, C., Bachstetter, A.D., 2013. The role of microglia in adult hippocampal neurogenesis. Front. Cell. Neurosci. 7, 229.
Ghasemi-Kasman, M., Hajikaram, M., Baharvand, H., Javan, M., 2015. MicroRNA-Mediated In Vitro and In Vivo Direct Conversion of Astrocytes to Neuroblasts. PLoS One 10 (6), e0127878.
Ghasemi-Kasman, M., Zare, L., Baharvand, H., Javan, M., 2017. In vivo conversion of astrocytes to myelinating cells by miR-302/367 and valproate to enhance myelin repair. J. Tissue Eng. Regen. Med.(2017 Jan 27). https://doi.org/10.1002/term.2276.
Ghasemi-Kasman, M., Shojaei, A., Gol, M., Moghadamnia, A.A., Baharvand, H., Javan, M., 2018. miR-302/367-induced neurons reduce behavioral impairment in an experimental model of Alzheimer's disease. Mol. Cell. Neurosci. 86, 50–57.
Grande, A., Sumiyoshi, K., López-Juárez, A., Howard, J., Sakthivel, B., Aronow, B., Campbell, K., Nakafuku, M., 2013. Environmental impact on direct neuronal reprogramming in vivo in the adult brain. Nat. Commun. 4, 2373.
Guo, F., Maeda, Y., Ma, J., Xu, J., Horiuchi, M., Miers, L., Vaccarino, F., Pleasure, D., 2010. Pyramidal neurons are generated from oligodendroglial progenitor cells in adult piriform cortex. J. Neurosci. 30 (36), 12036–12049.
Guo, Z., Zhang, L., Wu, Z., Chen, Y., Wang, F., Chen, G., 2014. In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell 14 (2), 188–202.
Hackett, A.R., Lee, J.K., 2016. Understanding the NG2 Glial Scar after Spinal Cord Injury. Front. Neurol. 7, 199.
Hama, H., Hara, C., Yamaguchi, K., Miyawaki, A., 2004. PKC signaling mediates global enhancement of excitatory synaptogenesis in neurons triggered by local contact with astrocytes. Neuron 41 (3), 405–415.
Heinrich, C., Blum, R., Gascón, S., Masserdotti, G., Tripathi, P., Sánchez, R., Tiedt, S., Schroeder, T., Götz, M., Berninger, B., 2010. Directing astroglia from the cerebral cortex into subtype specific functional neurons. PLoS Biol. 8 (5), e1000373.
Heinrich, C., Bergami, M., Gascón, S., Lepier, A., Viganò, F., Dimou, L., Sutor, B., Berninger, B., Götz, M., 2014. Sox2-mediated conversion of NG2 glia into induced neurons in the injured adult cerebral cortex. Stem Cell Reports 3 (6), 1000–1014.
Heins, N., Malatesta, P., Cecconi, F., Nakafuku, M., Tucker, K.L., Hack, M.A., Chapouton, P., Barde, Y.A., Götz, M., 2002. Glial cells generate neurons: the role of the transcription factor Pax6. Nat. Neurosci. 5 (4), 308–315.
Hesp, Z.C., Yoseph, R.Y., Suzuki, R., Jukkola, P., Wilson, C., Nishiyama, A., McTigue, D.M., 2018. Proliferating NG2-Cell-Dependent Angiogenesis and Scar Formation Alter Axon Growth and Functional Recovery After Spinal Cord Injury in Mice. J. Neurosci. 38 (6), 1366–1382.
Hoeffel, G., Ginhoux, F., 2018. Fetal monocytes and the origins of tissue-resident macrophages. Cell. Immunol. (18), 30001–30007 (pii S0008-8749).
Honsa, P., Valny, M., Kriska, J., Matuskova, H., Harantova, L., Kirdajova, D., Valihrach, L., Androvic, P., Kubista, M., Anderova, M., 2016. Generation of reactive astrocytes from NG2 cells is regulated by sonic hedgehog. Glia 64 (9), 1518–1531.
Hu, J.G., Lü, H.Z., Wang, Y.X., Bao, M.S., Zhao, B.M., Zhou, J.S., 2010. BMP signaling mediates astrocyte differentiation of oligodendrocyte progenitor cells. Tohoku J. Exp. Med. 222 (3), 195–200.
Huang, Y., Dreyfus, C.F., 2016. The role of growth factors as a therapeutic approach to demyelinating disease. Exp. Neurol. 283, 531–540 Pt B.
Huang, S., Ge, X., Yu, J., Han, Z., Yin, Z., Li, Y., Chen, F., Wang, H., Zhang, J., Lei, P., 2018. Increased miR-124-3p in microglial exosomes following traumatic brain injury inhibits neuronal inflammation and contributes to neurite outgrowth via their transfer into neurons. FASEB J. 32 (1), 512–528.
Hughes, E.G., Kang, S.H., Fukaya, M., Bergles, D.E., 2013. Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain. Nat. Neurosci. 16, 668–676.
Itoh, N., Itoh, Y., Tassoni, A., Ren, E., Kaito, M., Ohno, A, Ao., Y, Farkhondeh, V., Johnsonbaugh, H., Burda, J., Sofroniew, M.V., Voskuhl, R.R., 2018. Cell-specific and region-specific transcriptomics in the multiple sclerosis model: Focus on astrocytes. Proc. Natl. Acad. Sci. U. S. A. 115(2), E302-E309.
Janowska, J., Ziemka-Nalecz, M., Sypecka, J., 2018. The Differentiation of Rat

Oligodendroglial Cells Is Highly Influenced by the Oxygen Tension: In Vitro Model Mimicking Physiologically Normoxic Conditions. Int. J. Mol. Sci. 19 (2) (pii: E331.).
Jha, M.K., Kim, J.H., Song, G.J., Lee, W.H., Lee, I.K., Lee, H.W., An, S.S.A., Kim, S., Suk, K., 2018. Functional dissection of astrocyte-secreted proteins: Implications in brain health and diseases. Prog. Neurobiol. 162, 37–69.
Jorstad, N.L., Wilken, M.S., Grimes, W.N., Wohl, S.G., VandenBosch, L.S., Yoshimatsu, T., Wong, R.O., Rieke, F., Reh, T.A., 2017. Stimulation of functional neuronal regeneration from Müller glia in adult mice. Nature 548 (7665), 103–107.
Jovičić, A., Gitler, A.D., 2017. Distinct repertoires of microRNAs present in mouse astrocytes compared to astrocyte-secreted exosomes. PLoS One 12 (2), e0171418.
Jung, S., Panchalingam, K.M., Wuerth, R.D., Rosenberg, L., Behie, L.A., 2012. Large-scale production of human mesenchymal stem cells for clinical applications. Biotechnol. Appl. Biochem. 59 (2), 106–120.
Kessaris, N., Fogarty, M., Iannarelli, P., Grist, M., Wegner, M., Richardson, W.D., 2006. Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. Nat. Neurosci. 9 (2), 173–179.
Kettenmann, H., Kirchhoff, F., Verkhratsky, A., 2013. Microglia: new roles for the synaptic stripper. Neuron 77 (1), 10–18.
Khazaei, M., Ahuja, C.S., Fehlings, M.G., 2017. Generation of Oligodendrogenic Spinal Neural Progenitor Cells From Human Induced Pluripotent Stem Cells. Curr Protoc Stem Cell Biol. 14 (42) (2D.20.1-2D.20.14).
Kondo, T., Raff, M., 2004. Chromatin remodeling and histone modification in the conversion of oligodendrocyte precursors to neural stem cells. Genes Dev. 18 (23), 2963–2972.
Koniusz, S., Andrzejewska, A., Muraca, M., Srivastava, A.K., Janowski, M., Lukomska, B., 2016. Extracellular Vesicles in Physiology, Pathology, and Therapy of the Immune and Central Nervous System, with Focus on Extracellular Vesicles Derived from Mesenchymal Stem Cells as Therapeutic Tools. Front. Cell. Neurosci. 10, 109.
Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., Moryś, J., 2018. BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. Cell. Mol. Neurobiol. 38 (3), 579–593.
Kriegstein, A., Alvarez-Buylla, A., 2009. The glial nature of embryonic and adult neural stem cells. Annu. Rev. Neurosci. 32, 149–184.
Kronenberg, G., Gertz, K., Cheung, G., Buffo, A., Kettenmann, H., Götz, M., Endres, M., 2010. Modulation of fate determinants Olig2 and Pax6 in resident glia evokes spiking neuroblasts in a model of mild brain ischemia. Stroke 41 (12), 2944–2949.
Kucher, K., Johns, D., Maierm, D., Abelm, R., Badke, A., Baron, H., Thietje, R., Casha, S., Meindl, R., Gomez-Mancilla, B., Pfister, C., Rupp, R., Weidner, N., Mir, A., Schwab, M.E., Curt, A., 2018. First-in-Man Intrathecal Application of Neurite Growth-Promoting Anti-Nogo-A Antibodies in Acute Spinal Cord Injury. Neurorehabil. Neural Repair 1https://doi.org/10.1177/1545968318776371. (1545968318776371).
Kurachi, M., Mikuni, M., Ishizaki, Y., 2016. Extracellular Vesicles from Vascular Endothelial Cells Promote Survival, Proliferation and Motility of Oligodendrocyte Precursor Cells. PLoS One 11 (7), e0159158.
Küspert, M., Wegner, M., 2016. SomethiNG 2 talk about-Transcriptional regulation in embryonic and adult oligodendrocyte precursors. Brain Res. 1638(Pt B) 167–182.
Lai, S.W., Chen, J.H., Lin, H.Y., Liu, Y.S., Tsai, C.F., Chang, P.C., Lu, D.Y., Lin, C., 2018. Regulatory effects of neuroinflammatory responses through brain-derived neurotrophic factor signaling in microglial cells. Mol. Neurobiol. https://doi.org/10.1007/s12035-018-0933-z. (2018 Feb 9).
Lalo, U., Rasooli-Nejad, S., Pankratov, Y., 2014. Exocytosis of gliotransmitters from cortical astrocytes: implications for synaptic plasticity and aging. Biochem. Soc. Trans. 42 (5), 1275–1281.
Le Dréau, G., Martí, E., 2012. Dorsal-ventral patterning of the neural tube: a tale of three signals. Dev. Neurobiol. 72 (12), 1471–1481.
Leoni, G., Rattray, M., Butt, A.M., 2009. NG2 cells differentiate into astrocytes in cerebellar slices. Mol. Cell. Neurosci. 42 (3), 208–218.
Levi, G., Agresti, C., D'Urso, D., Aloisi, F., 1991. Is the oligodendroglial differentiation of bipotential oligodendrocyte-type 2 astrocyte progenitors promoted by autocrine factors? Neurosci. Lett. 128 (1), 37–41.
Li, X.J., Du, Z.W., Zarnowska, E.D., Pankratz, M., Hansen, L.O., Pearce, R.A., Zhang, S.C., 2005. Specification of motoneurons from human embryonic stem cells. Nat. Biotechnol. 23 (2), 215–221.
Lindvall, O., Rehncrona, S., Gustavii, B., Brundin, P., Astedt, B., Widner, H., Lindholm, T., Björklund, A., Leenders, K.L., Rothwell, J.C., Frackowiak, R., Marsden, C.D., Johnels, B., Steg, G., Freedman, R., Hoffer, B.J., Seiger, L., Strömberg, I., Bygdeman, M., Olson, L., 1988. Fetal dopamine-rich mesencephalic grafts in Parkinson's disease. Lancet 2 (8626-8627), 1483–1484.
Liu, X.S., Chopp, M., Kassis, H., Jia, L.F., Hozeska-Solgot, A., Zhang, R.L., Chen, C., Cui, Y.S., Zhang, Z.G., 2012. Valproic acid increases white matter repair and neurogenesis after stroke. Neuroscience 220, 313–321.
Liu, Y., Miao, Q., Yuan, J., Han, S., Zhang, P., Li, S., Rao, Z., Zhao, W., Ye, Q., Geng, J., Zhang, X., Cheng, L., 2015. Ascl1 Converts Dorsal Midbrain Astrocytes into Functional Neurons In Vivo. J. Neurosci. 35 (25), 9336–9355.
Liu, X.S., Chopp, M., Pan, W.L., Wang, X.L., Fan, B.Y., Zhang, Y., Kassis, H., Zhang, R.L., Zhang, X.M., Zhang, Z.G., 2017. MicroRNA-146a Promotes Oligodendrogenesis in Stroke. Mol. Neurobiol. 54 (1), 227–237.
Lloyd, A.F., Davies, C.L., Miron, V.E., 2017. Microglia: origins, homeostasis, and roles in myelin repair. Curr. Opin. Neurobiol. 47, 113–120.
Lugert, S., Basak, O., Knuckles, P., Haussler, U., Fabel, K., Gotz, M., Giachino, C., 2010. Quiescent and active hippocampal neural stem cells with distinct morphologies respond selectively to physiological and pathological stimuli and aging. Cell Stem Cell 6, 445–456.
Lukovic, D., Valdés-Sanchez, L., Sanchez-Vera, I., Moreno-Manzano, V., Stojkovic, M., Bhattacharya, S.S., Erceg, S., 2014. Brief report: astrogliosis promotes functional recovery of completely transected spinal cord following transplantation of hESC-derived oligodendrocyte and motoneuron progenitors. Stem Cells 32 (2), 594–599.
Luo, J., Daniels, S.B., Lennington, J.B., Notti, R.Q., Conover, J.C., 2006. The aging neurogenic subventricular zone. Aging Cell 5, 139–152.
Lupo, G., Nisi, P.S., Esteve, P., Paul, Y.L., Novo, C.L., Sidders, B., Khan, M.A., Biagioni, S., Liu, H.K., Bovolenta, P., Cacci, E., Rugg-Gunn, P.J., 2018 Mar. 2018. Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline. Aging Cell 5. https://doi.org/10.1111/acel.12745.
Lyck, L., Santamaria, I.D., Pakkenberg, B., Chemnitz, J., Schrøder, H.D., Finsen, B., Gundersen, H.J., 2009. An empirical analysis of the precision of estimating the numbers of neurons and glia in human neocortex using a fractionator-design with sub-sampling. J. Neurosci. Methods 182 (2), 143–156.
Ma, S., Kwon, H.J., Huang, Z., 2012. A functional requirement for astroglia in promoting blood vessel development in the early postnatal brain. PLoS One 7, e48001.
Magaki, S.D., Williams, C.K., Vinters, H.V., 2018. Glial function (and dysfunction) in the normal & ischemic brain. Neuropharmacology 134, 218–225 Pt B.
Masserdotti, G., Gillotin, S., Sutor, B., Drechsel, D., Irmler, M., Jørgensen, H.F., Sass, S., Theis, F.J., Beckers, J., Berninger, B., Guillemot, F., Götz, M., 2015. Transcriptional Mechanisms of Proneural Factors and REST in Regulating Neuronal Reprogramming of Astrocytes. Cell Stem Cell 17 (1), 74–88.
Mathiisen, T.M., Lehre, K.P., Danbolt, N.C., Ottersen, O.P., 2010. The perivascular astroglial sheath provides a complete covering of the brain microvessels: an electron microscopic 3D reconstruction. Glia 58 (9), 1094–1103.
Mazaheri, F., Breus, O., Durdu, S., Haas, P., Wittbrodt, J., Gilmour, D., Peri, F., 2014. Distinct roles for BAI1 and TIM-4 in the engulfment of dying neurons by microglia. Nat. Commun. 5, 4046.
McCoy, C.E., 2017. miR-155 Dysregulation and Therapeutic Intervention in Multiple Sclerosis. Adv. Exp. Med. Biol. 1024, 111–131.
Medina-Rodríguez, E.M., Bribián, A., Boyd, A., Palomo, V., Pastor, J., Lagares, A., Gil, C., Martínez, A., Williams, A., de Castro, F., 2017. Promoting in vivo remyelination with small molecules: a neuroreparative pharmacological treatment for Multiple Sclerosis. Sci. Rep. 7, 43545.
Meletis, K., Barnabé-Heider, F., Carlén, M., Evergren, E., Tomilin, N., Shupliakov, O., Frisén, J., 2008. Spinal cord injury reveals multilineage differentiation of ependymal cells. PLoS Biol. 6 (7), e182. https://doi.org/10.1371/journal.pbio.0060182.
Meyer, N., Richter, N., Fan, Z., Siemonsmeier, G., Pivneva, T., Jordan, P., Steinhäuser, C., Semtner, M., Nolte, C., Kettenmann, H., 2018. Oligodendrocytes in the Mouse Corpus Callosum Maintain Axonal Function by Delivery of Glucose. Cell Rep. 22(9), 2383-2394.
Miyamoto, A., Wake, H., Ishikawa, A.W., Eto, K., Shibata, K., Murakoshi, H., Koizumi, S., Moorhouse, A.J., Yoshimura, Y., Nabekura, J., 2016. Microglia contact induces synapse formation in developing somatosensory cortex. Nat. Commun. 7, 12540.
Mo, J.L., Liu, Q., Kou, Z.W., Wu, K.W., Yang, P., Chen, X.H., Sun, F.Y., 2018. MicroRNA-365 modulates astrocyte conversion into neuron in adult rat brain after stroke by targeting Pax6. Glia(2018 Feb 16). https://doi.org/10.1002/glia.23308.
Moreno-Manzano, V., Rodríguez-Jiménez, F.J., García-Roselló, M., Laínez, S., Erceg, S., Calvo, M.T., Ronaghi, M., Lloret, M., Planells-Cases, R., Sánchez-Puelles, J.M., Stojkovic, M., 2009. Activated spinal cord ependymal stem cells rescue neurological function. Stem Cells 27 (3), 733–743.
Mosher, K.I., Schaffer, D.V., 2018. Influence of hippocampal niche signals on neural stem cell functions during aging. Cell Tissue Res. 371 (1), 115–124.
Mothe, A.J., Tator, C.H., 2005. Proliferation, migration, and differentiation of endogenous ependymal region stem/progenitor cells following minimal spinal cord injury in the adult rat. Neuroscience 131 (1), 177–187.
Nakamura-Ishizu, A., Kurihara, T., Okuno, Y., Ozawa, Y., Kishi, K., Goda, N., Tsubota, K., Okano, H., Suda, T., Kubota, Y., 2012. The formation of an angiogenic astrocyte template is regulated by the neuroretina in a HIF-1-dependent manner. Dev. Biol. 363, 106–114.
Naruse, M., Ishino, Y., Kumar, A., Ono, K., Takebayashi, H., Yamaguchi, M., Ishizaki, Y., Ikenaka, K., Hitoshi, S., 2016. The Dorsoventral Boundary of the Germinal Zone is a Specialized Niche for the Generation of Cortical Oligodendrocytes during a Restricted Temporal Window. Cereb. Cortex 26 (6), 2800–2810.
Nathan, F.M., Li, S., 2017. Environmental cues determine the fate of astrocytes after spinal cord injury. Neural Regen. Res. 12 (12), 1964–1970.
Neumann, H., Kotter, M.R., Franklin, R.J.M., 2009. Debris clearance by microglia: an essential link between degeneration and regeneration. Brain 132, 288–295.
Niu, W., Zang, T., Zou, Y., Fang, S., Smith, D.K., Bachoo, R., Zhang, C.L., 2013. In vivo reprogramming of astrocytes to neuroblasts in the adult brain. Nat. Cell Biol. 15 (10), 1164–1175.
Niu, W., Zang, T., Smith, D.K., Vue, T.Y., Zou, Y., Bachoo, R., Johnson, J.E., Zhang, C.L., 2015. SOX2 reprograms resident astrocytes into neural progenitors in the adult brain. Stem Cell Reports 4 (5), 780–794.
Noctor, S.C., Flint, A.C., Weissman, T.A., Wong, W.S., Clinton, B.K., Kriegstein, A.R., 2002. Dividing precursor cells of the embryonic cortical ventricular zone have morphological and molecular characteristics of radial glia. J. Neurosci. 22, 3161–3173.
Noristani, H.N., Sabourin, J.C., Boukhaddaoui, H., Chan-Seng, E., Gerber, Y.N., Perrin, F.E., 2016. Spinal cord injury induces astroglial conversion towards neuronal lineage. Mol Neurodegener. 6 11 (1), 68.
Okada, S., Hara, M., Kobayakawa, K., Matsumoto, Y., Nakashima, Y., 2018. Astrocyte reactivity and astrogliosis after spinal cord injury. Neurosci. Res. 126, 39–43.
Ophelders, D.R., Wolfs, T.G., Jellema, R.K., Zwanenburg, A., Andriessen, P., Delhaas, T., Ludwig, A.K., Radtke, S., Peters, V., Janssen, L., Giebel, B., Kramer, B.W., 2016. Mesenchymal stromal cell-derived extracellular vesicles protect the fetal brain after hypoxia-ischemia. Stem Cells Transl. Med. 5, 754–763.
Panayiotou, E., Malas, S., 2013. Adult spinal cord ependymal layer: a promising pool of quiescent stem cells to treat spinal cord injury. Front. Physiol. 4, 340.

Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. Science 333 (6048), 1456–1458.
Parkhurst, C.N., Yang, G., Ninan, I., Savas, J.N., Yates 3rd, J.R., Lafaille, J.J., Hempstead, B.L., Littman, D.R., Gan, W.B., 2013. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155 (7), 1596–1609.
Paul, A., Chaker, Z., Doetsch, F., 2017. Hypothalamic regulation of regionally distinct adult neural stem cells and neurogenesis. Science 356 (6345), 1383–1386.
Peppard, J.V., Rugg, C.A., Smicker, M.A., Powers, E., Harnish, E., Prisco, J., Cirovic, D., Wright, P.S., August, P.R., Chandross, K.J., 2015. High-content phenotypic screening and triaging strategy to identify small molecules driving oligodendrocyte progenitor cell differentiation. J. Biomol. Screen. 20 (3), 382–390.
Pereira, M., Birtele, M., Shrigley, S., Benitez, J.A., Hedlund, E., Parmar, M., Ottosson, D.R., 2017. Direct Reprogramming of Resident NG2 Glia into Neurons with Properties of Fast-Spiking Parvalbumin-Containing Interneurons. Stem Cell Reports 9 (3), 742–751.
Perlow, M.J., Freed, W.J., Hoffer, B.J., Seiger, A., Olson, L., Wyatt, R.J., 1979. Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 204, 643–647.
Philips, T., Rothstein, J.D., 2017. Oligodendroglia: metabolic supporters of neurons. J. Clin. Invest. 127 (9), 3271–3280.
Pires, A.O., Mendes-Pinheiro, B., Teixeira, F.G., Anjo, S.I., Ribeiro-Samy, S., Gomes, E.D., Serra, S.C., Silva, N.A., Manadas, B., Sousa, N., Salgado, A.J., 2016. Unveiling the Differences of Secretome of Human Bone Marrow Mesenchymal Stem Cells, Adipose Tissue-Derived Stem Cells, and Human Umbilical Cord Perivascular Cells: A Proteomic Analysis. Stem Cells Dev. 25 (14), 1073–1083.
Ponomarev, E.D., Veremeyko, T., Weiner, H.L., 2013. MicroRNAs are universal regulators of differentiation, activation, and polarization of microglia and macrophages in normal and diseased CNS. Glia 61 (1), 91–103.
Quraishe, S., Forbes, L.H., Andrews, M.R., 2018. The Extracellular Environment of the CNS: Influence on Plasticity, Sprouting, and Axonal Regeneration after Spinal Cord Injury. Neural Plast. 18, 2952386.
Reick, C., Ellrichmann, G., Tsai, T., Lee, D.H., Wiese, S., Gold, R., Saft, C., Linker, R.A., 2016. Expression of brain-derived neurotrophic factor in astrocytes - Beneficial effects of glatiramer acetate in the R6/2 and YAC128 mouse models of Huntington's disease. Exp. Neurol. 285(Pt A) 12–23.
Rivers, L.E., Young, K.M., Rizzi, M., Jamen, F., Psachoulia, K., Wade, A., Kessaris, N., Richardson, W.D., 2008. PDGFRA/NG2 glia generate myelinating oligodendrocytes and piriform projection neurons in adult mice. Nat. Neurosci. 11 (12), 1392–1401.
Rivetti di Val Cervo, P., Romanov, R.A., Spigolon, G., Masini, D., Martín-Montañez, E., Toledo, E.M., La Manno, G., Feyder, M., Pifl, C., Ng, Y.H., Sánchez, S.P., Linnarsson, S., Wernig, M., Harkany, T., Fisone, G., Arenas, E., 2017. Induction of functional dopamine neurons from human astrocytes in vitro and mouse astrocytes in a Parkinson's disease model. Nat. Biotechnol. 35 (5), 444–452.
Robins, S.C., Trudel, E., Rotondi, O., Liu, X., Djogo, T., Kryzskaya, D., Bourque, C.W., Kokoeva, M.V., 2013. Evidence for NG2-glia derived, adult-born functional neurons in the hypothalamus. PLoS One 8 (10), e78236.
Rose, C.R., Felix, L., Zeug, A., Dietrich, D., Reiner, A., Henneberger, C., 2018. Astroglial Glutamate Signaling and Uptake in the Hippocampus. Front. Mol. Neurosci. 10, 451.
Rowitch, D.H., Kriegstein, A.R., 2010. Developmental genetics of vertebrate glial-cell specification. Nature 468 (7321), 214–222.
Ruffini, F., Arbour, N., Blain, M., Olivier, A., Antel, J.P., 2004. Distinctive properties of human adult brain-derived myelin progenitor cells. Am. J. Pathol. 165 (6), 2167–2175.
Ruppert, K.A., Nguyen, T.T., Prabhakara, K.S., Toledano Furman, N.E., Srivastava, A.K., Harting, M.T., Cox Jr., C.S., Olson, S.D., 2018. Human Mesenchymal Stromal Cell-Derived Extracellular Vesicles Modify Microglial Response and Improve Clinical Outcomes in Experimental Spinal Cord Injury. Sci. Rep. 8 (1), 480.
Sabelström, H., Stenudd, M., Frisén, J., 2014. Neural stem cells in the adult spinal cord. Exp. Neurol. 260, 44–49.
Saika, R., Sakuma, H., Noto, D., Yamaguchi, S., Yamamura, T., Miyake, S., 2017. MicroRNA-101a regulates microglial morphology and inflammation. J. Neuroinflammation 14 (1), 109.
Salgado, A.J., Sousa, J.C., Costa, B.M., Pires, A.O., Mateus-Pinheiro, A., Teixeira, F.G., Pinto, L., Sousa, N., 2015. Mesenchymal stem cells secretome as a modulator of the neurogenic niche: basic insights and therapeutic opportunities. Front. Cell. Neurosci. 9, 249.
Salvi, V., Sozio, F., Sozzani, S., Del Prete, A., 2017. Role of Atypical Chemokine Receptors in Microglial Activation and Polarization. Front. Aging Neurosci. 9, 148.
Sanchez, M.A., Armstrong, R.C., 2018. Postnatal Sonic hedgehog (Shh) responsive cells give rise to oligodendrocyte lineage cells during myelination and in adulthood contribute to remyelination. Exp. Neurol. 299(Pt A) 122–136.
Santello, M., Calì, C., Bezzi, P., 2012. Gliotransmission and the tripartite synapse. Adv. Exp. Med. Biol. 970, 307–331.
Schousboe, A., 2018. Metabolic signaling in the brain and the role of astrocytes in control of glutamate and GABA neurotransmission. Neurosci. Lett. pii S0304-3940 (18) (30044-2).
Shahbazi, E., Mirakhori, F., Ezzatizadeh, V., Baharvand, H., 2018. Reprogramming of somatic cells to induced neural stem cells. Methods 15 (133), 21–28.
Shen, S.W., Duan, C.L., Chen, X.H., Wang, Y.Q., Sun, X., Zhang, Q.W., Cui, H.R., Sun, F.Y., 2016. Neurogenic effect of VEGF is related to increase of astrocytes transdifferentiation into new mature neurons in rat brains after stroke. Neuropharmacology 108, 451–461.
Shigemoto-Mogami, Y., Hoshikawa, K., Goldman, J.E., Sekino, Y., Sato, K., 2014. Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone. J. Neurosci. 34 (6), 2231–2243.
Sierra, A., Encinas, J.M., Deudero, J.J., Chancey, J.H., Enikolopov, G., Overstreet-Wadiche, L.S., Tsirka, S.E., Maletic-Savatic, M., 2010. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 7 (4), 483–495.
Simon, C., Götz, M., Dimou, L., 2011. Progenitors in the adult cerebral cortex: cell cycle properties and regulation by physiological stimuli and injury. Glia 59 (6), 869–881.
Sims, N.R., Yew, W.P., 2017. Reactive astrogliosis in stroke: Contributions of astrocytes to recovery of neurological function. Neurochem. Int. 107, 88–103.
Sofroniew, M.V., 2014. Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neuroscientist 20 (2), 160–172.
Sofroniew, M.V., 2018. Dissecting spinal cord regeneration. Nature 557 (7705), 343–350.
Song, G.J., Suk, K., 2017. Pharmacological Modulation of Functional Phenotypes of Microglia in Neurodegenerative Diseases. Front. Aging Neurosci. 9, 139.
Su, Z., Niu, W., Liu, M.L., Zou, Y., Zhang, C.L., 2014. In vivo conversion of astrocytes to neurons in the injured adult spinal cord. Nat. Commun. 5, 3338.
Sung, S.C., Hong, J.L., Inja, L., Jun-ichi, S., Seung, U.K., 2014. Human Astrocytes: Secretome Profiles of Cytokines and Chemokines. PLoS One 9 (4), e92325.
Sur, M., Rubenstein, J.L.R., 2005. Patterning and plasticity of the cerebral cortex. Science 310, 805–810.
Sypecka, J., Sarnowska, A., 2013. Heterogeneity of local tissue microenvironment influences differentiation of oligodendroglial progenitors. Folia Neuropathol. 51 (2), 103–110.
Sypecka, J., Sarnowska, A., 2014. The neuroprotective effect exerted by oligodendroglial progenitors on ischemically impaired hippocampal cells. Mol. Neurobiol. 49 (2), 685–701.
Sypecka, J., Sarnowska, A., Domanska-Janik, K., 2009. Crucial role of the local microenvironment in fate decision of neonatal rat NG2 progenitors. Cell Prolif. 42 (5), 661–671.
Sypecka, J., Sarnowska, A., Gadomska-Szabłowska, I., Lukomska, B., Domańska-Janik, K., 2013. Differentiation of glia-committed NG2 cells: the role of factors released from hippocampus and spinal cord. Acta Neurobiol. Exp. (Wars) 73 (1), 116–129.
Sypecka, J., Ziemka-Nalecz, M., Dragun-Szymczak, P., Zalewska, T., 2017. A simple, xeno-free method for oligodendrocyte generation from human neural stem cells derived from umbilical cord: engagement of gelatinases in cell commitment and differentiation. J. Tissue Eng. Regen. Med. 11 (5), 1442–1455.
Takahashi, K., Yamanaka, S., 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126 (4), 663–676.
Tang, B.L., 2018. Patient-Derived iPSCs and iNs-Shedding New Light on the Cellular Etiology of Neurodegenerative Diseases. Cell 7 (5) (pii: E38).
Tang, Y., Le, W., 2016. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. Mol. Neurobiol. 53 (2), 1181–1194.
Tanner, D.C., Cherry, J.D., Mayer-Pröschel, M., 2011. Oligodendrocyte progenitors reversibly exit the cell cycle and give rise to astrocytes in response to interferon-γ J. Neurosci. 31 (16), 6235–6246.
Tapscott, S.J., Davis, R.L., Thayer, M.J., Cheng, P.F., Weintraub, H., Lassar, A.B., 1988. MyoD1: a nuclear phosphoprotein requiring a Myc homology region to convert fibroblasts to myoblasts. Science 242 (4877), 405–411.
Tatsumi, K., Isonishi, A., Yamasaki, M., Kawabe, Y., Morita-Takemura, S., Nakahara, K., Terada, Y., Shinjo, T., Okuda, H., Tanaka, T., Wanaka, A., 2018. Olig2-Lineage Astrocytes: A Distinct Subtype of Astrocytes That Differs from GFAP Astrocytes. Front. Neuroanat. 12, 8.
Teixeira, F.G., Panchalingam, K.M., Anjo, S.I., Manadas, B., Pereira, R., Sousa, N., Salgado, A.J., Behie, L.A., 2015. Do hypoxia/normoxia culturing conditions change the neuroregulatory profile of Wharton Jelly mesenchymal stem cell secretome? Stem Cell Res Ther 6, 133.
Torper, O., Ottosson, D.R., Pereira, M., Lau, S., Cardoso, T., Grealish, S., Parmar, M., 2015. In Vivo Reprogramming of Striatal NG2 Glia into Functional Neurons that Integrate into Local Host Circuitry. Cell Rep. 12 (3), 474–481.
Tripathi, R., McTigue, D.M., 2007. Prominent oligodendrocyte genesis along the border of spinal contusion lesions. Glia 2007 55 (7), 698–711.
Tripathi, R.B., Rivers, L.E., Young, K.M., Jamen, F., Richardson, W.D., 2010. NG2 glia generate new oligodendrocytes but few astrocytes in a murine experimental autoimmune encephalomyelitis model of demyelinating disease. J. Neurosci. 30 (48), 16383–16390.
Tsoa, R.W., Coskun, V., Ho, C.K., de Vellis, J., Sun, Y.E., 2014. Spatiotemporally different origins of NG2 progenitors produce cortical interneurons versus glia in the mammalian forebrain. Proc. Natl. Acad. Sci. U. S. A. 111 (20), 7444–7449.
Ullian, E.M., Sapperstein, S.K., Christopherson, K.S., Barres, B.A., 2001. Control of synapse number by glia. Science 291, 657–661.
Ulloa, F., Martí, E.,2010. Wnt won the war: antagonistic role of Wnt over Shh controls dorso-ventral patterning of the vertebrate neural tube. Dev. Dyn. 239(1), 69-76.
Vallstedt, A., Klos, J.M., Ericson, J., 2005. Multiple dorsoventral origins of oligodendrocyte generation in the spinal cord and hindbrain. Neuron 45, 55–67.
van Tilborg, E., de Theije, C.G.M., van Hal, M., Wagenaar, N., de Vries, L.S., Benders, M.J., Rowitch, D.H., Nijboer, C.H., 2018. Origin and dynamics of oligodendrocytes in the developing brain: Implications for perinatal white matter injury. Glia 66 (2), 221–238.
Vardjan, N., Zorec, R., 2015. Excitable astrocytes: Ca- and cAMP-regulated exocytosis. Neurochem. Res. 40, 2414–2424.
Verkhratsky, A., Matteoli, M., Parpura, V., Mothet, J.P., Zorec, R., 2016. Astrocytes as secretory cells of the central nervous system: idiosyncrasies of vesicular secretion. EMBO J. 35 (3), 239–257.
Volarevic, V., Markovic, B.S., Gazdic, M., Volarevic, A., Jovicic, N., Arsenijevic, N., Armstrong, L., Djonov, V., Lako, M., Stojkovic, M., 2018. Ethical and Safety Issues of Stem Cell-Based Therapy. Int. J. Med. Sci. 15 (1), 36–45.

Wake, H., Moorhouse, A.J., Jinno, S., Kohsaka, S., Nabekura, J., 2009. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J. Neurosci. 29 (13), 3974–3980.
Wang, L.L., Su, Z., Tai, W., Zou, Y., Xu, X.M., Zhang, C.L., 2016. The p53 Pathway Controls SOX2-Mediated Reprogramming in the Adult Mouse Spinal Cord. Cell Rep. 17 (3), 891–903.
Wang, X., Weng, M., Jin, Y., Yang, W., Wang, X., Wu, D., Wang, T., Li, X., 2018. Beyond an oncogene, Lin28 is a master regulator of cancer progression. Histol. Histopathol. 33 (4), 327–334.
Weber, B., Barros, L.F., 2015. The Astrocyte: Powerhouse and Recycling Center. Cold Spring Harb. Perspect. Biol. 7 (12) (pii: a020396).
Wen, M.M., 2016. Getting miRNA Therapeutics into the Target Cells for Neurodegenerative Diseases: A Mini-Review. Front. Mol. Neurosci. 9, 129.
Wheeler, N.A., Fuss, B., 2016. Extracellular cues influencing oligodendrocyte differentiation and (re)myelination. Exp. Neurol. 283(Pt B) 512–530.
Wichterle, H., Lieberam, I., Porter, J.A., Jessell, T.M., 2002. Directed differentiation of embryonic stem cells into motor neurons. Cell 110 (3), 385–397.
Wilkins, A., Chandran, S., Compston, A., 2001. A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons. Glia 36 (1), 48–57.
Wilkins, A., Majed, H., Layfield, R., Compston, A., Chandran, S., 2003. Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. J. Neurosci. 23(12), 4967-4974.
Windrem, M.S., Nunes, M.C., Rashbaum, W.K., Schwartz, T.H., Goodman, R.A., McKhann 2nd, G., Roy, N.S., Goldman, S.A., 2004. Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. Nat. Med. 10 (1), 93–97.
Wolpaw, A.J., Dang, C.V., 2018. MYC-induced metabolic stress and tumorigenesis. Biochim Biophys Acta. In: pii: S0304-419X(18)30071-4.
Xia, X., Ahmad, I., 2016. Unlocking the Neurogenic Potential of Mammalian Müller Glia. Int J Stem Cells. 9 (2), 169–175.
Xiao, D., Qu, Y., Pan, L., Li, X., Mu, D., 2018. MicroRNAs participate in the regulation of oligodendrocytes development in white matter injury. Rev. Neurosci. 29 (2), 151–160.
Xin, H., Li, Y., Liu, Z., Wang, X., Shang, X., Cui, Y., Zhang, Z.G., Chopp, M., 2013. MiR-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells in rats via transfer of exosome-enriched extracellular particles. Stem Cells 31 (12), 2737–2746.
Xin, H., Katakowski, M., Wang, F., Qian, J.Y., Liu, X.S., Ali, M.M., Buller, B., Zhang, Z.G., Chopp, M., 2017. MicroRNA cluster miR-17-92 Cluster in Exosomes Enhance Neuroplasticity and Functional Recovery After Stroke in Rats. Stroke 48 (3), 747–753.
Yan, Y., Shin, S., Jha, B.S., Liu, Q., Sheng, J., Li, F., Zhan, M., Davis, J., Bharti, K., Zeng, X., Rao, M., Malik, N., Vemuri, M.C., 2013. Efficient and rapid derivation of primitive neural stem cells and generation of brain subtype neurons from human pluripotent stem cells. Stem Cells Transl. Med. 2 (11), 862–870. https://doi.org/10.5966/sctm.2013-0080.
Yang, N., Chanda, S., Marro, S., Ng, Y.H., Janas, J.A., Haag, D., Ang, C.E., Tang, Y., Flores, Q., Mall, M., Wapinski, O., Li, M., Ahlenius, H., Rubenstein, J.L., Chang, H.Y., Buylla, A.A., Südhof, T.C., Werning, M., 2017. Generation of pure GABAergic neurons by transcription factor programming. Nat. Methods 14 (6), 621–628.
Yin, G., Du, M., Li, R., Li, K., Huang, X., Duan, D., Ai, X., Yao, F., Zhang, L., Hu, Z., Wu, B., 2018. Glia maturation factor beta is required for reactive gliosis after traumatic brain injury in zebrafish. Exp. Neurol. 305, 129–138.
Yu, X., Odenthal, M., Fries, J.W., 2016. Exosomes as miRNA Carriers: Formation-Function-Future. Int. J. Mol. Sci. 17 (12) (pii: E2028).
Zarruk, J.G., Greenhalgh, A.D., David, S., 2018. Microglia and macrophages differ in their inflammatory profile after permanent brain ischemia. Exp. Neurol. 301(Pt B) 120–132.
Zeis, T., Enz, L., Schaeren-Wiemers, N., 2016. The immunomodulatory oligodendrocyte. Brain Res. 1641(Pt A) 139–148.
Zhang, L., Yin, J.C., Yeh, H., Ma, N.X., Lee, G., Chen, X.A., Wang, Y., Lin, L., Chen, L., Jin, P., Wu, G.Y., Chen, G., 2015. Small Molecules Efficiently Reprogram Human Astroglial Cells into Functional Neurons. Cell Stem Cell 17 (6), 735–747.
Zhang, J., Zhang, Z.G., Lu, M., Wang, X., Shang, X., Elias, S.B., Chopp, M., 2017a. MiR-146a promotes remyelination in a cuprizone model of demyelinating injury. Neuroscience 348, 252–263.
Zhang, M., Ma, Z., Qin, H., Yao, Z., 2017b. Monocarboxylate Transporter 1 in the Medial Prefrontal Cortex Developmentally Expresses in Oligodendrocytes and Associates with Neuronal Amounts. Mol. Neurobiol. 54 (3), 2315–2326.
Zhang, Y., Chopp, M., Zhang, Z.G., Katakowski, M., Xin, H., Qu, C., Ali, M., Mahmood, A., Xiong, Y., 2017c. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury. Neurochem. Int. 111, 69–81.
Zhao, J.W., Raha-Chowdhury, R., Fawcett, J.W., Watts, C., 2009. Astrocytes and oligodendrocytes can be generated from NG2+ progenitors after acute brain injury: intracellular localization of oligodendrocyte transcription factor 2 is associated with their fate choice. Eur. J. Neurosci. 29 (9), 1853–1869.
Zheng, G., Huang, R., Qiu, G., Ge, M., Wang, J., Shu, Q., Xu, J., 2018. Mesenchymal stromal cell-derived extracellular vesicles: regenerative and immunomodulatory effects and potential applications in sepsis. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2871-5. (2018 Jun 28).
Zhu, X., Bergles, D.E., Nishiyama, A., 2008. NG2 cells generate both oligodendrocytes and gray matter astrocytes. Development 135 (1), 145–157.
Ziemka-Nalecz, M., Jaworska, J., Sypecka, J., Polowy, R., Filipkowski, R.K., Zalewska, T., 2017. Sodium Butyrate, a Histone Deacetylase Inhibitor, Exhibits Neuroprotective/Neurogenic Effects in a Rat Model of Neonatal Hypoxia-Ischemia. Mol. Neurobiol. 54 (7), 5300–5318.
Zorec, R., Parpura, V., Verkhratsky, A., 2017. Astroglial Vesicular Trafficking in Neurodegenerative Diseases. Neurochem. Res. 42 (3), 905–917.