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Astrocytes as a source for extracellular matrix molecules and cytokines

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Research of the past 25 years has shown that astrocytes do more than participating and building up the blood-brain barrier and detoxify the active synapse by reuptake of neurotransmitters and ions. Indeed, astrocytes express neurotransmitter receptors and, as a consequence, respond to stimuli. Within the tripartite synapse, the astrocytes owe more and more importance. Besides the functional aspects the differentiation of astrocytes has gained a more intensive focus. Deeper knowledge of the differentiation processes during development of the central nervous system might help explaining and even help treating neurological diseases like Alzheimer's disease, Amyotrophic lateral sclerosis, Parkinsons disease, and psychiatric disorders in which astrocytes have been shown to play a role. Specific differentiation of neural stem cells toward the astroglial lineage is performed as a multi-step process. Astrocytes and oligodendrocytes develop from a multipotent stem cell that prior to this has produced primarily neuronal precursor cells. This switch toward the more astroglial differentiation is regulated by a change in receptor composition on the cell surface and responsiveness to Fibroblast growth factor and Epidermal growth factor (EGF). The glial precursor cell is driven into the astroglial direction by signaling molecules like Ciliary neurotrophic factor, Bone Morphogenetic Proteins, and EGF. However, the early astrocytes influence their environment not only by releasing and responding to diverse soluble factors but also express a wide range of extracellular matrix (ECM) molecules, in particular proteoglycans of the lectican family and tenascins. Lately these ECM molecules have been shown to participate in glial development. In this regard, especially the matrix protein Tenascin C (Tnc) proved to be an important regulator of astrocyte precursor cell proliferation and migration during spinal cord development. Nevertheless, ECM molecules expressed by reactive astrocytes are also known to act mostly in an inhibitory fashion under pathophysiological conditions. Thus, we further summarize resent data concerning the role of chondroitin sulfate proteoglycans and Tnc under pathological conditions.

Keywords: astroglial development, extracellular matrix, Tenascin-c, cytokines, reactive astrocytes

INTRODUCTION

When the neuroglial cells were first described, these cells were thought to act as connective cells that subdivide neurons into clusters of cells in the brain, spinal cord, and nerves (Virchow, 1856). Later this connective tissue was named glia ("glue") that can be distinguished from nerve cells within the brain and the peripheral nervous system (PNS). Glial cells include primarily oligodendrocytes and astrocytes in the central nervous system (CNS) and Schwann cells in the PNS. In addition, the brain "immune cells," the microglia are the immune competent macrophages of the CNS (Kauppinen et al., 1989; Volterra and Meldolesi, 2005; De Keyser et al., 2008; Allen and Barres, 2009; Kettenmann and Verkhratsky, 2011). While oligodendrocytes and Schwann cells mainly function as myelin producing cells ensheathing the axon in the central and PNS, the astrocytes have long been thought to have a structural function, providing energy, detoxifying the synapses, and building up the blood-brain barrier, rather than an active role in neurotransmission (Kettenmann and Verkhratsky, 2011). Astrocytes represent the major brain cell component (20–50%). They send out numerous processes and locally contact the surrounding cells, neurons, other glial cells, and endothelial cells. Besides the pure barrier function, they also play a vital role in the control of cerebral blood flow and the glucose homeostasis of the brain as this is the main energy source for the brain. For review (see Sofroniew and Vinters, 2009).

Within the developing brain and spinal cord Neural stem cell precursor cells (NSPCs) generate neuronal cells in the first place. Changes in the expression of growth factor receptors subsequently result in the specification of astroglial cells (see also **Table 1**). Here, it has been shown that the expression of the epidermal growth factor (EGF)-Receptor seems to be necessary for normal astrocyte development (Kornblum et al., 1998). While initial PDGF and FGF2 signals form these cells the cells themselves turn to a PDGF-R negative precursor cell (see also **Figure 1**). In general, the cells are then characterized by expression of A2B5, Nestin and PLP, and the fibroblast growth factor (FGF)-Receptor.

Table 1 | Stage dependent marker expression for the astroglial differentiation lineage.

Marker	Early precursor cell	Late precursor cell	Astrocyte precursor	Mature astrocyte	Citations
Nestin	+	+	−	−	Rauch et al. (1997), Kornblum et al. (1998)
BLBP	+	+	−	−	Rauch et al. (1997), Kornblum et al. (1998)
FGFR	+	+	−	−	Kornblum et al. (1998)
GLAST	−	+	+	+	Lehre et al. (1995)
EGFR	−	+	+ ?	−	Karus et al. (2011)
Tnc	−	+	+	−	Lehre et al. (1995), Karus et al. (2011)
FGFR3	−	−	+	+	Cahoy et al. (2008)
S100β	−	−	+	+	Nagelhus et al. (2004)
Aqp4	−	−	+	+	Nagelhus et al. (2004)
AldH1L1	−	−	+	+	Cahoy et al. (2008)
GFAP	−	−	−	+	Meeuwsen et al. (2003)

BLBP, basic lipid binding protein; FGFR/FGFR3, Fibroblast growth factor receptor (3); GLAST, Glutamate-Aspartate Transporter; EGFR, Epidermal growth factor receptor; Tnc, Tenascin C; Aqp4, Aquaporin 4; AldH1L1, Aldehyde dehydrogenase 1, member L1; GFAP, Glial fibrillary acidic protein.

The maturation of astrocytes is also accompanied by the expression of a wide variety of chondroitin sulfate proteoglycans (CSPGs) like brevican, neurocan, versican and aggrecan, and extracellular matrix (ECM) proteins, namely Tnc, that are released to the ECM compartment but have also impact on the astrocytes themselves. This gains importance as the glial scar has been shown to reexpress, e.g., Tnc that can highly influence the regenerative capacity to its worse in Human and mammals (Sofroniew and Vinters, 2009). In this review we will therefore first focus on the development of astrocytes in the CNS with respect to functions of the ECM therein and then take a closer look to functional aspects of soluble factors and ECM molecules in health and disease.

THE NEURAL EXTRACELLULAR MATRIX: COMPOSITION AND FUNCTIONAL ASPECTS FOR ASTROCYTE DEVELOPMENT

Cells in connective tissues are embedded in an ECM that not only binds the cells together but also influences their survival, development, shape, polarity, and behavior. The ECM includes various protein fibers interwoven in a hydrated gel (Maleski and Hockfield, 1997; Rauch et al., 1997). In general this interwoven meshwork comprises fibrillar proteins (e.g., collagens), glycoproteins (e.g., laminins, fibronectin, tenascins), and several classes of proteoglycans (heparan sulfate-, chondroitin sulfate-, dermatan sulfate-, and keratan sulfate proteoglycans). The latter mainly consist of large glycosaminoglycan (GAG) chains, covalently linked to extracellular or membrane bound core proteins. In contrast to other tissues, the ECM in the CNS lacks fibrillar proteins under physiological conditions. Instead the neural ECM is rich in glycoproteins and proteoglycans. It has been estimated that the neural ECM makes up about 20% of the CNS parenchyma (Nicholson and Sykova, 1998). Therefore, it is not surprising, that several studies in the last decades demonstrated important functions of distinct ECM molecules in the developing as well as in the adult CNS. During the early development of the CNS the overall expression of ECM molecules is relatively low and subsequently increases toward the end of embryogenesis and during postnatal development. However, the germinal layers already contain distinct ECM components and their cognate receptors during neurogenesis in the developing cortex (Ford-Perriss et al., 2003; von Holst et al., 2006; Lathia et al., 2007; Moritz et al., 2008). In the adult CNS several ECM molecules are prominently expressed in stem cell niches (Gates et al., 1995; von Holst et al., 2006; Kazanis et al., 2007).

RADIAL GLIA STEM CELLS AND NEUROSPHERES EXPRESS CSPGs AND ECM MOLECULES

Despite their prominent expression during neural development only little is known about the functional importance of specific CSPGs and ECM molecules for astrocyte development. In the following we summarize recent findings concerning the roles of CSPGs and members of the Tenascin family in the context of the cortical and spinal cord development. CSPGs consist of chondroitin sulfate GAG chains, covalently attached to a serine residue of a core protein (Kleene and Schachner, 2004). CSPGs have been shown to bind to FGF2 and modulate FGF signaling (Milev et al., 1998; Sirko et al., 2010a). Thus, they are perfectly suited for regulating neural development.

When exploring the ECM structure in the stem cell niche, we have shown in an earlier study that both phosphacan and the DSD-1-epitope are enriched in the germinal zones of the adult CNS (Gates et al., 1995). Therefore, we have more closely examined the relationship of the DSD-1- (473HD-) epitope to the neural stem cell compartment during different stages of development. We provided evidence that both Neural stem cell precursor cells (NSPCs) and radial glia express the RPTP-β/ζ-receptor and the 473HD-carbohydrate (Garwood et al., 2001; Faissner et al., 2006; von Holst et al., 2006). The structure targeted by monoclonal antibody (MAb) 473HD is enriched in the germinal layers during mouse forebrain development and can be considered a novel surface marker of radial glia (von Holst et al., 2006). This is consistent with the observation that CSPGs are released by NSPCs growing as neurospheres (Ida et al., 2006). Neurospheres are viewed as culture model of NSPCs that grow in suspension and comprise neural stem and committed progenitor cells. The neurospheres strongly express the 473HD-epitope. Consistent with this observation, a compositional analysis detected a considerable variety of mono- and di-sulfated disaccharide units in chondroitin sulfate/dermatan sulfate (CS/DS) chains purified from the embryonic mammalian CNS (Ueoka et al., 2000; Zou et al., 2003; Bao et al., 2005; Properzi

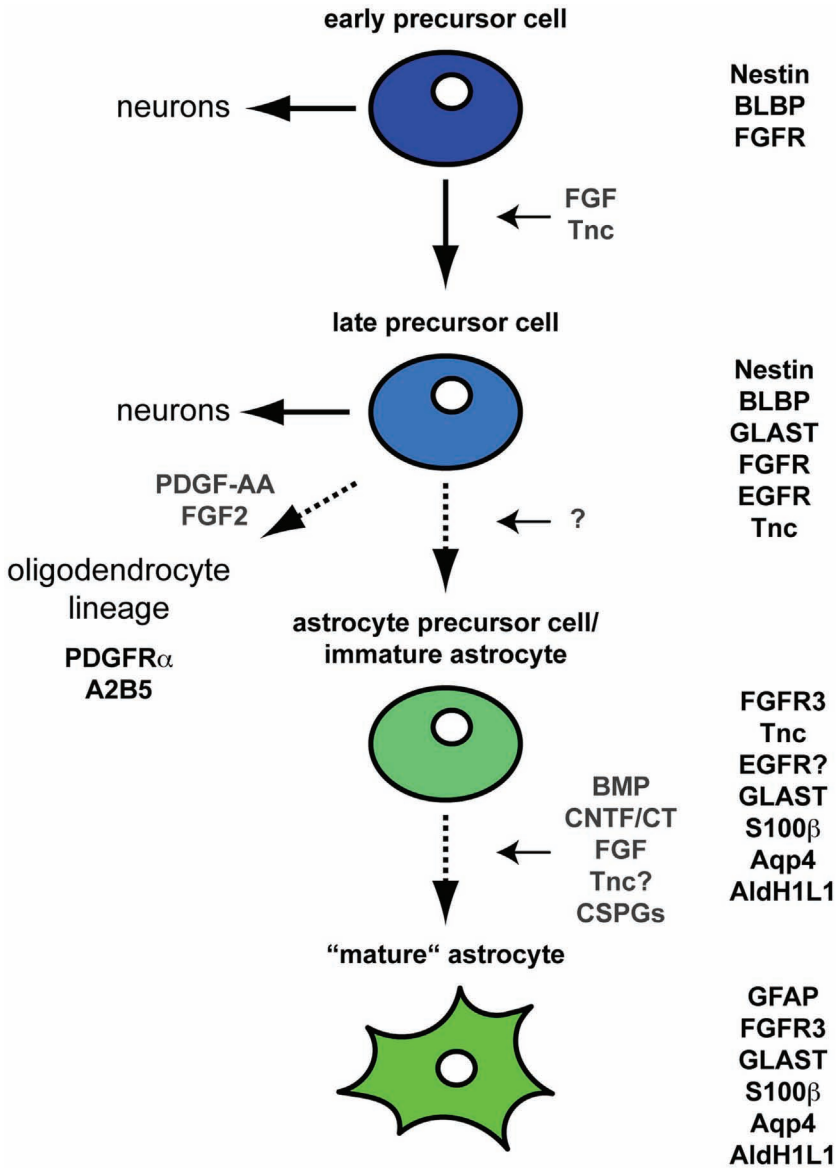

FIGURE 1 | Differentiation of astrocytes during CNS development Schematic illustration of the CNS astroglial lineage and its associated molecular markers. At early embryonic stages NSPCs expressing Nestin, BLBP, and FGFRs primarily generate neurons. Upon sustained FGF signaling these NSPCs acquire an additional EGF responsiveness. The expression of the EGFR is also stimulated by Tnc (Karus et al., 2011). At that stage NPCs still generate neurons through intermediate progenitors at least in the embryonic cortex. In contrast, these EGF responsive NPCs appear to generate only few if any neurons in the embryonic spinal cord. Regardless of their location along the rostro-caudal axis these NPCs already share some molecular markers with astroglial cells such as GLAST and Tnc (Lehre et al., 1995). These cells also express additional markers such as S100β, Aquaporin 4 (Nagelhus et al., 2004), Fibroblast growth factor receptor 3 (FGFR3), and Aldh1L1 (Cahoy et al., 2008). Subsequently the cells transform into GFAP-positive mature astrocytes often classified into fibrous white matter and protoplasmic gray matter astrocytes. In this context, soluble molecules such as CNTF/CT1, BMPs, and FGFs are known to regulate the GFAP expression (Meeuwsen et al., 2003). Moreover, CSPGs and potentially also Tnc are also involved in the maturation toward GFAP-positive astrocytes (Sirko et al., 2007).

et al., 2005; Ida et al., 2006). CSPGs as well as CS specific sulfotransferases are expressed by both radial glia cells in the embryonic cortex and NSPCs cultivated as free floating neurospheres (Kabos et al., 2004; von Holst et al., 2006; Akita et al., 2008; Ishii and Maeda, 2008). To obtain functional insights into potential functions of the 473HD-epitope, the MAb 473HD, or the enzyme chondroitinase ABC (ChABC) were added to neurosphere cultures. Both treatments caused a reduction of the number of neurospheres and proliferating NSPCs (von Holst et al., 2006; Sirko et al., 2010b). Furthermore, the treatment with ChABC treatment favored the generation of the astrocyte lineage at the expense of neurogenesis (Sirko et al., 2007, 2010a). Altogether, these data clearly suggest that CS-GAGs are involved in controlling the pathway of NSPC expansion and differentiation.

The enzymes that are required for the biosynthesis of CS-GAGs sulfation patterns are detectable in neurospheres and in neurogenic regions of the developing and the adult CNS (Akita et al., 2008). With regard to astrocyte development, chicken embryos lacking the CSPG aggrecan exhibit an increased differentiation of astrocyte precursors toward GFAP-positive astrocytes (Domowicz et al., 2008). Along these lines the enzymatic degradation of CS-GAGs from telencephalic NSPCs promotes astroglial differentiation *in vitro* and *in vivo* (Sirko et al., 2007).

Besides CSPGs members of the Tenascin gene family recently gained much attention with regard to glial development owing to their late embryonic and early postnatal expression (Czopka et al., 2009; Karus et al., 2011). We have recently shown that Tnc regulates the maturation of astroglial cells during embryonic spinal cord development, primarily by orchestrating the growth factor responsiveness of NSPCs (**Figure 1**; Karus et al., 2011). This appears to be a common phenomenon, since a Tnc dependent regulation of growth factor responsiveness has also been shown for cortical NPCs (Garcion et al., 2004; Yagi et al., 2010). Tnc also modifies the expression of important neural patterning genes at the onset of gliogenesis in the developing spinal cord. However, on a cell biological level, the lack of Tnc affects gliogenic NSPC proliferation and migration (see also **Figure 2**; Karus et al., 2011). The effect on gliogenic NSPC proliferation is in line with a former report on primary human astrocytes, showing a Tnc dependent reduction in BrdU incorporation accompanied by reduced Nestin expression levels (Holley et al., 2005). In addition, Tnc lowers the Nestin expression level of rat NSPC derived astrocytes (Nash et al., 2011). Interestingly, both the adult cortex and the adult hippocampus of Tnc deficient animals contain more S100β-positive astrocytes (Irintchev et al., 2005; Gurevicius et al., 2009). These phenotypes could be explained by changes of astrocyte proliferation and differentiation during development.

MATURE ASTROCYTES EXPRESS, RELEASE, AND REGULATE PROTEOGLYCAN EXPRESSION IN HEALTH AND DISEASE

Astrocytes express a large range of proteoglycans (see also **Figure 2**), both during development and after lesion, under which condition they contribute significantly to the glial scar. The proteoglycans are generally subdivided into two classes, the membrane-associated heparin sulfate proteoglycans (HSPGs) of the glypican and the syndecan subfamilies; and CSPGs of the lectican family such as brevican, neurocan, versican, and aggrecan that are mostly released into the extracellular environment

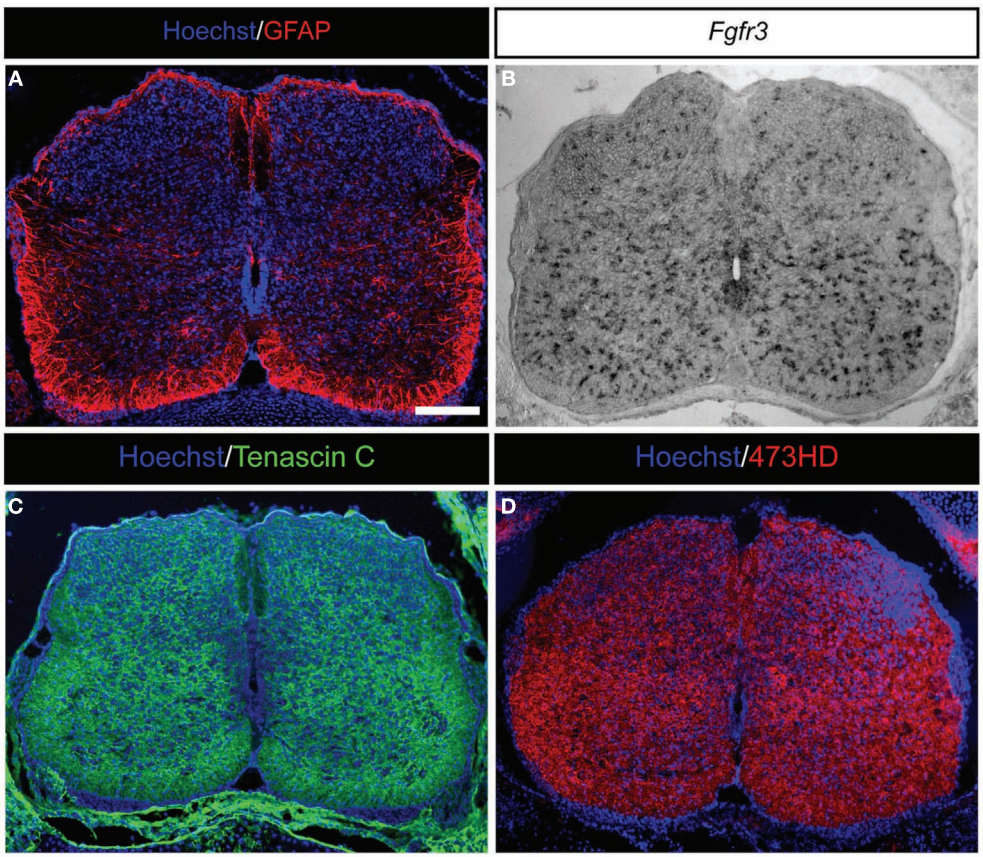

FIGURE 2 | Expression of astrocyte markers and ECM molecules in the developing mouse spinal cord. (A) GFAP-positive astrocytes in the developing E18.5 mouse spinal cord are present predominantly in the white matter and within the later gray matter as migrating cells. **(B)** Moreover, Fgfr3-expressing astroglial cells are distributed throughout the whole spinal cord. **(C)** Additionally, the spinal cord is characterized by strong expression of ECM molecules, such as the glycoprotein Tenascin C or **(D)** glycosaminoglycans residues on proteoglycans detected by the mAb473HD. Scale bar: 100 μm.

(Bandtlow and Zimmermann, 2000). HSPGs play important roles in FGF-2-signaling by recruiting the cytokine to its receptor FGFR. Furthermore, they have been implicated in supporting the signal transfer of morphogens such as Wnt-proteins that regulate neural stem cell proliferation.

Chondroitin sulfate proteoglycans are enriched in CNS scar tissue after lesions and thought to inhibit regeneration of axons (Smith-Thomas et al., 1994, 1995; Silver and Miller, 2004; Carulli et al., 2005; Properzi et al., 2005; Busch and Silver, 2007; Fitch and Silver, 2008; Galtrey et al., 2008; Kwok et al., 2008). In agreement with this view, the elimination of CSPGs with the bacterial enzyme ChABC improves functional recovery in the CNS after damage (Bradbury et al., 2002;Fawcett, 2006a,b; Fitch and Silver, 2008; Massey et al., 2008). The regeneration preventing properties of CSPGs and the potential therapeutic value of ChABC have been extensively commented in recent years (Verma et al., 2008; Fawcett, 2009). Yet, ChABC resistant inhibition has also been reported (Siddiqui et al., 2009). Beyond a role as obstacles to regeneration, CSPGs have also been implicated in the regulation of synaptic plasticity (Bradbury et al., 2002; Pizzorusso et al., 2002; Faissner et al., 2010). In this context the 473HD-epitope has been shown to be expressed on a subpopulation of GFAP- as well as nestin-positive cells in a laser lesion model of the adult rat visual cortex. Therefore, the 473HD-epitope as stem cell-marker designates the cells which generate the neurospheres that can be cultivated from the lesioned adult rat cortex (Sirko et al., 2009). This particular chondroitin sulfate motif has been discovered with the help of a MAb recognizing the 473HD-epitope (Faissner et al., 1994a; Gates et al., 1995). The structure has been designated as DSD-1-epitope, which is strongly enriched on phosphacan (Garwood et al., 1999, 2001). The DSD-1-glycosaminoglycan (GAG)-epitope is functionally active in that it promotes neurite outgrowth from several CNS neuron types (Faissner et al., 1994b; Garwood et al., 1999). The structural analysis revealed that the 473HD- (synonymous to DSD-1-) epitope requires sulfation and comprises the CS-D-type chondroitin sulfate motif (Faissner et al., 1994b; Clement et al., 1998; Nadanaka et al., 1998; Hikino et al., 2003). Overall, the structure is characterized by sulfated hexa- or octasaccharide oligomers that differ from the binding sites of the monoclonal anti-chondroitin sulfate antibodies CS-56 or MO-225 (Ito et al., 2005).

THE ECM GLYCOPROTEIN TENASCIN-C IS EXPRESSED AND REGULATED BY DEVELOPING AND REACTIVE ASTROCYTES

Tenascin-C is a glycoprotein that is expressed in the ECM of various tissues where it regulates processes such as cell growth, migration, and adhesion during development (see also **Figure 2**), but also under pathological conditions in the adult, for example in tumors (Faissner, 1997a; Jones and Jones, 2000; Joester and Faissner, 2001; Chiquet-Ehrismann and Chiquet, 2003; Chiquet-Ehrismann and Tucker, 2011). Tnc is even involved in plasticity, memory, and learning by modulation of L-type Ca^{2+} channels and modulation via the fibronectin domains (Evers et al., 2002; Strekalova et al., 2002). Tnc is built up in a modular fashion and consists of a cysteine-rich amino-terminus, Egf-like domains followed by fibronectin type III (FNIII) domains and a carboxyterminal domain resembling fibrinogen-b. The smallest Tnc variant contains a sequence of eight FNIII repeats that are included in all Tnc proteins. A large number of isoforms can be generated by the inclusion of up to six (mouse), seven (rat, Garwood et al., 2012), or nine (human) additional alternatively spliced FNIII domains between the fifth and sixth FNIII domains of the basic structure. In mice, up to 27 Tnc-isoforms have been described so far, suggesting a combinatorial code (Joester and Faissner, 1999; von Holst et al., 2007). The alternatively spliced domains A1, A2, A4, B, C, and D expressed in mouse encode diverse functions by themselves, which indicates that the combinatorial variation is functionally relevant (Faissner, 1997b; Joester and Faissner, 2001; Tucker et al., 2006). It is tempting to speculate that binding and availability of the EGF might depend on the splice variants of Tnc as structural folding might also change the availability of the bound EGF. This could lead to direct changes in the amounts of EGF in the intracellular space and therefore lead to changes in the response to this factor.

In the developing CNS, Tnc is first expressed by radial glia and later primarily by astrocytes, where it seems to exert autocrine effects that regulate the proliferation of astrocyte progenitor cells (Karus et al., 2011). Tnc modulates the stem cell compartment in the niche, where it is specifically enriched in the environment of mouse NSPCs at embryonic day E14–E15 (von Holst et al., 2007). For example, tenascin-C contributes to the maturation of NSPCs (Garcion et al., 2004) and to the proliferation and maintenance of oligodendrocyte precursors (Garcion et al., 2001; Garwood et al., 2004; Czopka et al., 2009). The gene Sam68 is a Tnc-regulated target and involved in the control of NSPC proliferation (Moritz et al., 2008). *In vivo* and *in vitro* studies demonstrate that Tnc encodes permissive as well as inhibitory cues and thereby mediates neuron migration and axon growth and guidance in the context of neuron-glia interactions (Faissner and Kruse, 1990; Lochter et al., 1991; Husmann et al., 1992;Götz et al., 1996, 1997; Meiners and Geller, 1997; Meiners et al., 1999).

Tnc expression is down-regulated in the adult CNS, with the exception of the canonic neurogenic zones and regions of plasticity in the hypothalamus (Theodosis et al., 1997). In stab wound and knife-cut injuries, however, a subset of GFAP-positive reactive astrocytes up-regulate Tnc (McKeon et al., 1991; Laywell et al., 1992; Brodkey et al., 1995; Zhang et al., 1997; Tang et al., 2003; Dobbertin et al., 2010). Interestingly, the transcription factor Pax6 is also expressed in CNS lesions (Sirko et al., 2009) and induces the preferential up-regulation of the large alternatively spliced Tnc-isoforms *in vitro* (von Holst et al., 2007). Enhanced Tnc expression is also observed in gliomas, in non-invasive laser lesions (Sirko et al., 2009), in the dentate gyrus after unilateral entorhinal cortex lesion (Deller et al., 1997) or the hippocampus after injection of kainic acid (Niquet et al., 1995; Nakic et al., 1996). The cytokines FGF2 and TGF-β that have been implicated in scar formation both induce Tnc expression in astrocyte cultures (Meiners et al., 1993; Mahler et al., 1997; Smith and Hale, 1997; Flanders et al., 1998; Smith et al., 2001). The question whether distinct isoform variants are selectively regulated has been examined in detail in knife cut wounds inflicted in the adult CNS, an established forebrain injury model. While the small isoform dominated in the resting CNS we observed a 25-fold injury-induced increase of the spliced paired TNfnBD-containing isoforms. Interestingly, transforming

growth factor-β1 (TGF-β1) as well as TGF-β1 in conjunction with FGF2 induced a strong increase of D-containing Tnc isoforms in the ECM of astrocyte monolayers in culture (Dobbertin et al., 2010).

FUNCTIONAL IMPLICATIONS OF UP-REGULATION OF Tnc IN CENTRAL NERVOUS SYSTEM WOUNDS

The expression of the large Tnc-isoforms correlates with periods of increased axonal growth in the developing CNS (Prieto et al., 1990; Bartsch et al., 1992; Joester and Faissner, 2001). Most of the Tnc splice variants in the developing brain contain the FNIII domain TNfnD which promotes neurite outgrowth in all neurons tested so far (Götz et al., 1996; Rigato et al., 2002; Siddiqui et al., 2008; Michele and Faissner, 2009). A peptide encoded in domain TNfnD has been reported to stimulate axon growth in an α7β1 integrin-dependent manner (Meiners et al., 2001; Mercado et al., 2004). Thus, the enrichment of Tnc isoforms containing the TNfnBD or TNfnD6 domains may create an environment favorable to axonal growth. This interpretation is consistent with a recent study reporting that Tnc retards retrograde degeneration in a spinal cord injury model and that the TNfnD-domain is required for this effect (Chen et al., 2010; Yu et al., 2011).

On the other hand, Tnc alternating with laminin-1 stripes exerts a strong repulsive effect on growth cones at the boundary separating it from the promoting substrate in a choice assay (Faissner and Kruse, 1990; Taylor et al., 1993; Götz et al., 1996). Using domains heterologously expressed in bacteria we could show that both the TNegf-type repeats and the alternatively spliced $TNfnA_1A_2A_4$ domains are repulsive in this assay (Götz et al., 1996). Consistent with these observations, sprouting axons do not penetrate the Tnc-rich denervated outer molecular layer of the rat fascia dentate after entorhinal lesion (Deller et al., 1997). Tnc-up-regulation has also been proposed to inhibit terminal sprouting of mossy fibers in kainate-treated hippocampus (Niquet et al., 1995). Boundaries formed by Tnc-containing ECM have also been observed in developing tissues (Faissner and Steindler, 1995; Treloar et al., 2009).

SOLUBLE FACTORS INFLUENCING ASTROCYTES IN HEALTH AND DISEASE

Astrocytes can secrete and respond to a number of important cytokines affecting the cellular state of surrounding cells, such as microglia and neurons, and astrocytes themselves. Factors, such as Interleukin-6 (IL-6), Interleukin-1β (IL-1β), TGF-β1, and Tumor necrosis factor α (TNFα) can act to up regulate or down regulate other pro- and anti-inflammatory genes including COX-2 and NOS-2. Astrocytes also play an important role in secretion of trophic factors such as glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), or basic fibroblast growth factor (bFGF or FGF2). Astrocytes can promote neuronal and oligodendrocyte survival by secretion of such factors and can also promote myelination and thereby influence maturation of oligodendrocytes. Therefore, analysis and targeting of growth factor release to promote survival and maintenance of adjacent cells like neurons is an important function that still has to be further analyzed. Here, we further focus on the role of the activated signaling cascades that may have impact on diseases concerning the released factors of astrocytes.

CNTF, IL-6, AND STAT3 SIGNALING

Ciliary neurotrophic factor (CNTF) is a cytokine that can be produced by glia of the CNS and PNS and in terms of signaling can be mimicked in its action (Stöckli et al., 1989, 1991) CNTF signals through the LIF-Receptor-β/gp130 receptor, which, among others elicits activation of the JAK/Stat pathway and therefore leads to changes in gene expression mainly through the activation of STAT3 (Nakashima et al., 1999). Activation of STAT3 through only gp130 by Interleukin-6 (IL-6) signaling is known to trigger reactive astrogliosis (Sofroniew, 2009). The role of IL-6 is ambivalent, depending on the animal model and the disease that occurs in the experimental paradigms (Campbell et al., 1993; Penkowa et al., 2003; Quintana et al., 2009).

STAT3 is an early trigger for astrogliosis in astrocytes (Sriram et al., 2004). In a mouse model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced striatal degeneration, gp130-related cytokines (e.g., IL-6, CNTF) were up regulated prior to STAT3 activation and nuclear translocation. These events also involve up regulation of GFAP expression, and GFAP mRNA and protein therefore can be used as a marker in astrogliosis (Nakashima et al., 1999; Yanagisawa et al., 1999). STAT3 is not the only trigger for astrogliosis, but it seems to be required for it to occur, at least in the case of spinal cord injury. Ablating STAT3 signals in astrocytes as a consequence leads to attenuated GFAP expression and diminishes astrocyte glial scar formation, compared with *Stat3* wild type astrocytes in mice (Herrmann et al., 2008). In this light, experiments ablating STAT3 in neurons showing that motoneuron survival is significantly reduced after facial nerve lesion in the adult (Schweizer et al., 2002) might also be influenced by less active astrocytes as the astrocytes might have been less activated by missing signals from the lesioned motoneurons. Overall, further study of CNTF, IL-6, and STAT3 signaling pathways might be interesting as it further clarifies the concert interaction of astrocytes, other glial cells, and last not least neurons.

GDNF SIGNALING

Astrocytes are the major source for GDNF upon brain injury (Bresjanac and Antauer, 2000; Nakagawa and Schwartz, 2004). It also may be responsible for maintenance of GDNF levels in the substantia nigra of Parkinson patients (Mogi et al., 2001). Therefore it may also contribute to a survival scenario toward neuronal survival. While neuronal expression of GDNF under pathophysiological conditions appears to be uncontrollable and widespread also toward the contralateral side of a lesioned brain, astrocytic expression of GDNF exerts a strictly local function (Drinkut et al., 2011). Especially GDNF shows an application dependent function as intrathecal injection of the factor did not significantly improve late stage Parkinsons disease (PD) patients (Lang et al., 2006; Marks et al., 2010), while astrocytic delivery of GDNF proved to be efficient at least in a mouse model (Drinkut et al., 2011). Local administration of neurotrophic support therefore appears to be a possible solution to the general problem of administration of trophic factors that in the past caused various side effects or proved to be insufficient (Sendtner et al., 1995; Ochs et al., 2000).

NF-κB SIGNALING

NF-κB is a mediator of transcriptional induction for various inflammatory cytokines/factors like IL-6 (Spooren et al., 2010) and NOS-2. It translocates to the nucleus, and binds to its NF-κB consensus sequence. NF-κB can be activated by pro-inflammatory mediators, including LPS, TNFα, and IL-1β. The classical and endogenous activator is IL-1β. Inhibition of NF-κB in astrocytes is reported to ameliorate inflammation and improves recovery after spinal cord injury (Brambilla et al., 2005).

TGF-β1 AND SMAD SIGNALING

The cytokine TGF-β1 is generally expressed at low to undetectable levels in the brain, but it is strongly up regulated under neuropathological conditions in various neurologic diseases (Kiefer et al., 1993a,b, 1995; Morgan et al., 1993; Wang et al., 1995; Peress et al., 1996; Vawter et al., 1996; Ata et al., 1997; Krupinski et al., 1998; De Groot et al., 1999; Ali et al., 2001; Zetterberg et al., 2004). TGF-β1 signals by binding to TGFβRII. The receptor heterodimerizes with and phosphorylates the TGFβ signaling receptor TGFβRI. It then activates activin-like kinase 5 or 1 (ALK5, ALK1), and initiates an intracellular serine/threonine kinase signaling cascade. While ALK1 phosphorylates SMAD1/5/8, ALK5 phosphorylates mothers against decapentaplegic homologs 2/3 (SMAD2/3) which results in nuclear translocation of signaling complexes that change gene expression pattern (Miyazawa et al., 2002).

The effects of TGF-β1 in the brain appear to be dependent on the disease which is examined. There are reports on the neuroprotective role of TGF-β1 as well as there are reports that show its pro-inflammatory and neuropathological role. In general the effects are widespread and appear to be context-dependent with respect to the disease or disorder examined. An extensive literature has clearly demonstrated a neuroprotective role (Prehn et al., 1993; Henrich-Noack et al., 1996; Mattson et al., 1997; Wyss-Coray et al., 1997;Burton et al., 2002a,b; Brionne et al., 2003; Buisson et al., 2003). Anyhow there is still a missing link for both of these roles with respect to astrocytic functions. However, TGF-β1 is known to have various effects on astrocytes, such as gene expression, or up-regulation of the amyloid precursor protein (APP; Amara et al., 1999; Burton et al., 2002a; Lesné et al., 2003) modulation of the astrocyte response to pro-inflammatory mediators (Hamby et al., 2006, 2008) and regulation of astrogliosis via increasing GFAP expression, eliciting hypertrophy, and facilitating glial scar formation through up regulation of ECM molecules (ECM; i.e., CSPGs, fibronectin, laminin; Smith and Strunz, 2005). These ECM molecules, especially the CSPGs produced by astrocytes have been investigated in concert with nerve cells to elucidate the diverse functional aspects in terms of neurite growth and survival. Sofar it is known by now that the protein core unit and the glycosaminoglycan chains as well as possibly also the sulfation of these molecules might have even contradictory impact on survival and neurite growth (Conrad et al., 2011; Klausmeyer et al., 2011). Consistent with the effects of TGF-β1 on ECM formation, mice that lack *Smad3*, the downstream effector of TGF-β1 signaling through ALK5, exhibit a faster rate of wound closure after stab injury to the brain, compared with control mice (Wang et al., 2007). Future elucidation of regulatory molecules in response to TGF-β1 signaling in the brain pathway should prove a more detailed picture of the concert activities and the role for astrocytes in this signaling concert.

NUCLEOTIDES AND THEIR RECEPTORS

In addition to their many essential intracellular functions, the nucleotides ATP, ADP, and adenosine have functions as extracellular signaling molecules. Nucleotides like ATP or ADP can exert their activities on various cell types within the body and they act through different specific plasma membrane receptors, the purinoceptors P2X and P2Y, and the adenosine receptors (Khakh and North, 2006). ATP signaling triggers elevation in cytosolic calcium in astrocytes (Bowser and Khakh, 2007; Halassa et al., 2009a; Shigetomi et al., 2010) may even function in sleep modulation influenced by astrocytes (Halassa et al., 2009b) and leads to gene expression changes associated with reactive astrogliosis after trauma-induced cell injury *in vitro* (Neary et al., 2003, 2004; Wanner et al., 2008). The molecular pharmacology of P2X, P2Y, and adenosine involves a number of inhibitors and activators, and some of these are being studied for effects on reactive astrogliosis and CNS injury and repair after traumatic injuries such as spinal cord injury (Wang et al., 2004; Peng et al., 2009). This will be a promising area for future exploration.

ASTROCYTIC FUNCTIONS IN NEUROLOGICAL DISEASES

Astroglial cells are involved in neurological diseases by determination of progression and outcome in neuropathological processes. Astrocytes are involved in various neurodegenerative diseases, including Alzheimer's disease (AD), PD, and amyotrophic lateral sclerosis (ALS; Harvey et al., 2010). Recent evidence suggests that early stages of neurodegenerative processes are accompanied with atrophy of astroglia, which causes disruptions in synaptic connectivity, misbalance in neurotransmitter homeostasis, and neuronal death. At later stages, astrocytes become activated and contribute to the neuroinflammatory component of neurodegeneration.

In the pathology of AD Aβ can act as a neurotoxic protein that disrupts calcium signaling in neurons and alters synaptic plasticity (Boillée et al., 2006; Vincent et al., 2010). These effects can lead to loss of synapses, and therefore a dysfunction in the neural network. Protection against AD therefore seems to be in part regulated by environmental cues like higher education. However, the precise mechanism by which Aβ causes neurodegeneration is still not clear. The role of astrocytes in early cognitive decline is a major component of disease pathology (Agostinho et al., 2010; Balducci and Forloni, 2010; Vincent et al., 2010). Aβ can disrupt astrocytic calcium signaling and gliotransmitter release, processes that are vital for astrocyte-neuron communication (Vincent et al., 2010). Therefore, astrocyte dysfunction may contribute to the earliest neuronal deficits in AD.

The role of astrocytes in the early pathogenesis of PD has not been fully characterized so far; but astrogliosis was detected at the late stages of the disease (McGeer and McGeer, 2008; Mena and García de Yébenes, 2008; Solano et al., 2008). At the same time the substantia nigra, in which PD pathology primarily develops, has a low density of astrocytes compared to other brain regions so that early astroglial atrophy and especially mitochondrial pathology

may have a pathological significance that has not been able to be completely understood so far (Stichel et al., 2007; Schmidt et al., 2011). Astrocyte degeneration can result in diminished support for dopaminergic neurons and therefore be associated with an increased vulnerability. However, this is still a hypothesis to be tested.

Neuron-glial interactions also play an important role in ALS pathology. Prominent astroglial degeneration and atrophy was found in the human SOD1G93A transgenic mouse model. The astrocyte degeneration included both neuronal death and the appearance of clinical symptoms (Rossi et al., 2008; Rossi and Volterra, 2009). The ALS astrocytes in mice (expressing the human SOD1) were more sensitive to glutamate, and displayed a glutamate excitotoxicity (Rossi et al., 2008; Rossi and Volterra, 2009). Even more important, the selective silencing of the SOD1 mutant gene in astrocytes significantly slowed the progression of ALS in transgenic mice (Yamanaka et al., 2008). Late stages of ALS are also characterized by significant astrogliosis and astrocyte proliferation (McGeer and McGeer, 2008).

OUTLOOK

Astrocytes and astrocyte development have gained more and more intensive research focus over the past years. The changes in view on these cells started with the switch to a more global view in terms of a tissue or organ and not in terms of a single cell type therein. Analysis of astrocyte development and changes that lead to specific alterations are of higher interest as pathological situations like lesions, toxic insults, or neurodegenerative diseases show – parallel to what has been shown for neurons already – that astrocytes reexpress markers that have been down regulated. The difference to neurons might be on the first sight the capacity to undergo cell division so that the cells primarily do not undergo apoptosis. Here, extracellular cues are of high importance as they give signals to the cells and may even regulate the availability of survival versus cell death signals by blocking or neutralizing specific factors. To further elucidate the concert action of soluble factors and matrix components that influence on the other hand the expression profile of the developing and mature astrocytes will be of high importance for the future research.

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