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Commentary

Astrocytes in the damaged brain: Molecular and cellular insights into their reactive response and healing potential

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ABSTRACT

Long considered merely a trophic and mechanical support to neurons, astrocytes have progressively taken the center stage as their ability to react to acute and chronic neurodegenerative situations became increasingly clear. Reactive astrogliosis starts when trigger molecules produced at the injury site drive astrocytes to leave their quiescent state and become activated. Distinctive morphological and biochemical features characterize this process (cell hypertrophy, upregulation of intermediate filaments, and increased cell proliferation). Moreover, reactive astrocytes migrate towards the injured area to constitute the glial scar, and release factors mediating the tissue inflammatory response and remodeling after lesion. A novel view of astrogliosis derives from the finding that subsets of reactive astrocytes can recapitulate stem cell/progenitor features after damage, fostering the concept of astroglia as a promising target for reparative therapies. But which biochemical/signaling pathways modulate astrogliosis with respect to both the time after injury and the type of damage? Are reactive astrocytes overall beneficial or detrimental for neuroprotection and tissue regeneration? This debate has been animating this research field for several years now, and an integrated view on the results obtained and the possible future perspectives is needed. With this Commentary article we have attempted to answer the above-mentioned questions by reviewing the current knowledge on the molecular mechanisms controlling and sustaining the reaction of astroglia to injury and its stem cell-like properties. Moreover, the cellular/molecular mechanisms supporting the detrimental or beneficial features of astrogliosis have been scrutinized to gain insights on possible pharmacological approaches to enhance astrocyte neuroprotective activities.

1. Introduction

Astrocytes are multifunctional cells that, in addition to play an essential homeostatic role and contribute to information processing in physiological conditions, are capable to mount a response to any kind of insult to the central nervous system (CNS). In their reaction to injury (astrogliosis) they leave their quiescent state and become activated. During this process, they undergo hypertrophy, upregulate intermediate filaments composed of nestin, vimentin, and glial fibrillary protein (GFAP), and activate cell proliferation (Fig. 1) [1,2] (see also below). Moreover, in their reactive state astrocytes can continue to divide, migrate to form the glial scar, and release a plethora of factors mediating the tissue inflammatory response and remodeling after lesion [3,4]. It is increasingly clear that the modalities and dynamics of the astrocyte response to damage are crucial to the outcome of brain pathology and the degree of neurological damage. In light of these facts, astrogliosis appears to be an appealing therapeutic target for the implementation of endogenous repair in the CNS.

Abbreviations: Ado, adenosine; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate; AP1, activator protein 1; AQP, acquaporin; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; bHLH, basic helix loop helix; BMP, bone morphogenetic protein; CNS, central nervous system; CNTF, ciliary neurotrophic factor; COX-2, cyclooxigenase-2; CREB, cAMP response element binding; CSPGs, chondroitinsulphate proteoglycans; ERK, extracellular signal-regulated kinase; EGF, epidermal growth factor; Eph4A, ephrin 4A; Epo, erythropoietin; ET1, Endothelin 1; ET-R, endothelin receptor; GABA, gamma-aminobutyric acid; GDNF, glial cell-line derived neurotrophic factor; GF, growth factor; GFAP, glial fibrillary acidic protein; GLAST, glutamate/aspartate transporter; GLT1, glutamate transporter 1; GS, glutamine synthase; IFNβ, interferon beta; IFNγ, interferon gamma; IGF1, insulin growth factor 1; IL1β, interleukin 1 beta; IL2, interleukin 2; IL6, interleukin 6; IL10, interleukin 10; JAK, Janus protein tyrosine kinases; Lcn2, Lipocalin 2; MAPK, mitogen-activated protein kinase; MMP, matrix metalloprotease; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cell; NFkB, nuclear factor kappa B; NGF, nerve growth factor; NT3, neurotrophin 3; p38MAPK, p38 mitogen-activated protein kinase; PTEN, phosphatase and tensin homolog; SOCS, suppressor of cytokine signaling; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TGFα, transforming growth factor alpha; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

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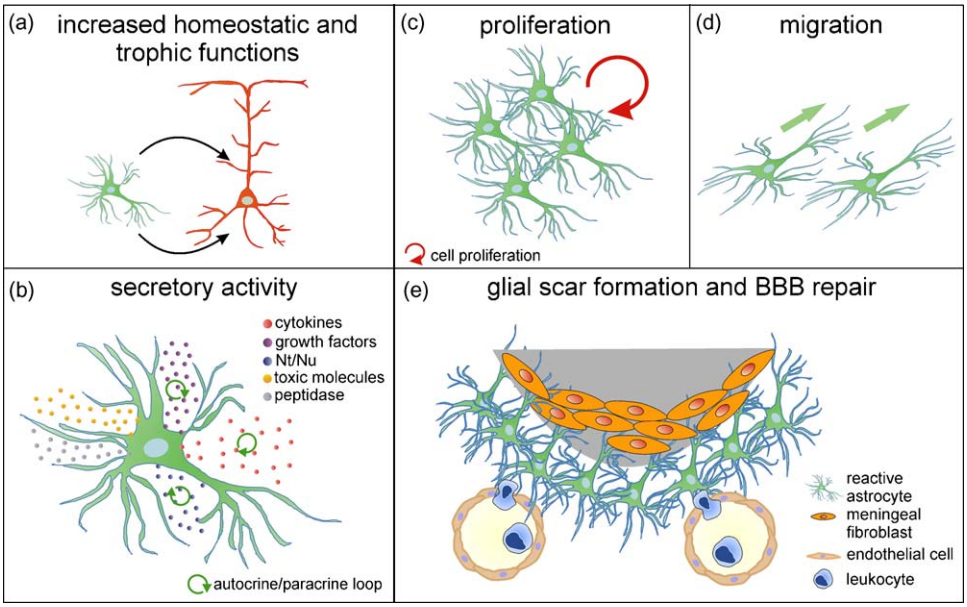

Fig. 1. Hallmarks of astrocyte reactivity. Upon CNS injury, activated astrocytes increase their homeostatic and trophic functions (a), the production of growth factors and cytokines, as well as the release of nucleotides and toxic compounds (b). Their secretion is regulated via complex autocrine and paracrine loops (b). Astrogliosis includes cell proliferation (c) and migration towards the lesion site (d). Reactive astrocytes participate in glial scar formation, and contribute to the resealing of the damaged blood–brain barrier, thus excluding infiltrating leukocytes and meningeal fibroblasts from the injured tissue (e). Nt/Nu, nucleotides/nucleosides; BBB, blood–brain barrier.

In this review we shall discuss the molecular mechanisms known to regulate astroglia activation and the evolution of the ensuing reactivity. Special focus will be devoted to highlight how functional changes in astroglia influence the lesioned nervous tissue either beneficially or detrimentally with respect to tissue integrity and functional outcome. Furthermore, we shall attempt to compose an integrated picture of this duality, and discuss how the novel stem cell/progenitor aspects of some astroglia subsets, together with the detailed understanding of gliosis regulatory mechanisms, may help in developing strategies for treating the insulted CNS.

2. Astrogliosis: molecular triggers and cellular response

Upon injury, the astroglia response is evoked by several changes occurring in the CNS parenchyma. These changes include the production of a variety of molecular signals (Fig. 2), partly derived by plasma extravasation, able to trigger the transition from the quiescent to the activated state or to modulate astrocyte reactivity over time. The distinction between activating and modulating signals remains in large undefined. However, very early triggers such as purines/pyrimidines and pro-inflammatory cytokines [5,6] are predominantly considered to evoke the initial astrocyte activation (although their release can be also maintained over time thus contributing to later responses). The major role of the later secondary mediators (e.g., endothelin, ET; growth factors, GFs; inflammatory molecules) may instead be to sustain the long-term features of astrogliosis until inhibitory molecules such as interferon beta (IFNβ), interleukin 10 (IL10), erythropoietin (Epo) begin to predominate over inductive triggers [7–9]. At this final stage, the resolution of gliosis leads to the reacquisition of quiescent morphological and functional features in astrocytes far from the source of injury (isomorphic gliosis), or to the stabilization of astroglia reactive traits in the form of a permanent glial scar close to the lesion site (anisomorphic gliosis) [3].

The molecular, temporal and functional interconnections amongst the various signaling pathways controlling astrocyte reactivity are extremely complex, and still largely unknown. Below we summarize what is currently known on these topics.

2.1. Extracellular signals

2.1.1. Purines and pyrimidines

ATP has been recently recognized as one of the most important molecules involved in CNS cell-to-cell communication and utilized to spread information between neurons and glial cells as well as between glial cells themselves [10]. Besides ATP, other purine (i.e., ADP) and pyrimidine (UTP, UDP, and UDP-sugars) nucleotides can contribute to intercellular communication by activating ligand-operated channels (the $P2X_{1-7}$ receptors) and G protein-coupled metabotropic receptors (the P2Y receptor family), currently encompassing 8 cloned subtypes ($P2Y_{1,2,4,6,11,12,13,14}$) with different agonist and antagonist selectivity profiles [11].

Where do nucleotides come from in the brain? ATP is co-stored in neuronal synaptic vesicles and therefore co-released with "classical" neurotransmitters, but it can also be released by astrocytes through vesicle shedding [12,13]. The physiological release of uracil nucleotides is still a matter of debate. However, given their active role in the glycosylation reactions, these compounds are likely to be released together with glycosylated proteins and peptidoglycans [14]. Uracil nucleotides could therefore represent important signaling molecules at sites enriched of glycosylated moieties, such as within the astrocytic glial scar (see also below).

Massive amounts of nucleotides are also released from damaged cells at early stages after traumatic and ischemic events, partly due to the leakage of cytoplasmic content from dying cells, but also as a consequence of the increased excitotoxic transmission (Fig. 2) [15], and of astrocyte exposure to plasma components (Fig. 1b) (e.g., thrombin; [16]). Thus, during emergencies astrocytes and surrounding cells are exposed to high micromolar nucleotide concentrations. Since astrocytes express the whole panel of P2Y receptors at the mRNA level, as well as the 7 ionotropic P2X subtypes [17], the purinergic system appears as a key modulator of the astrocytic response to injury.

Indeed, in vitro [18–20] and in vivo [21] evidence indicates that ATP and its analogs promote astrocytic proliferation and emission of long and branched GFAP-positive processes through the activation of specific G protein-coupled P2Y receptors. The same

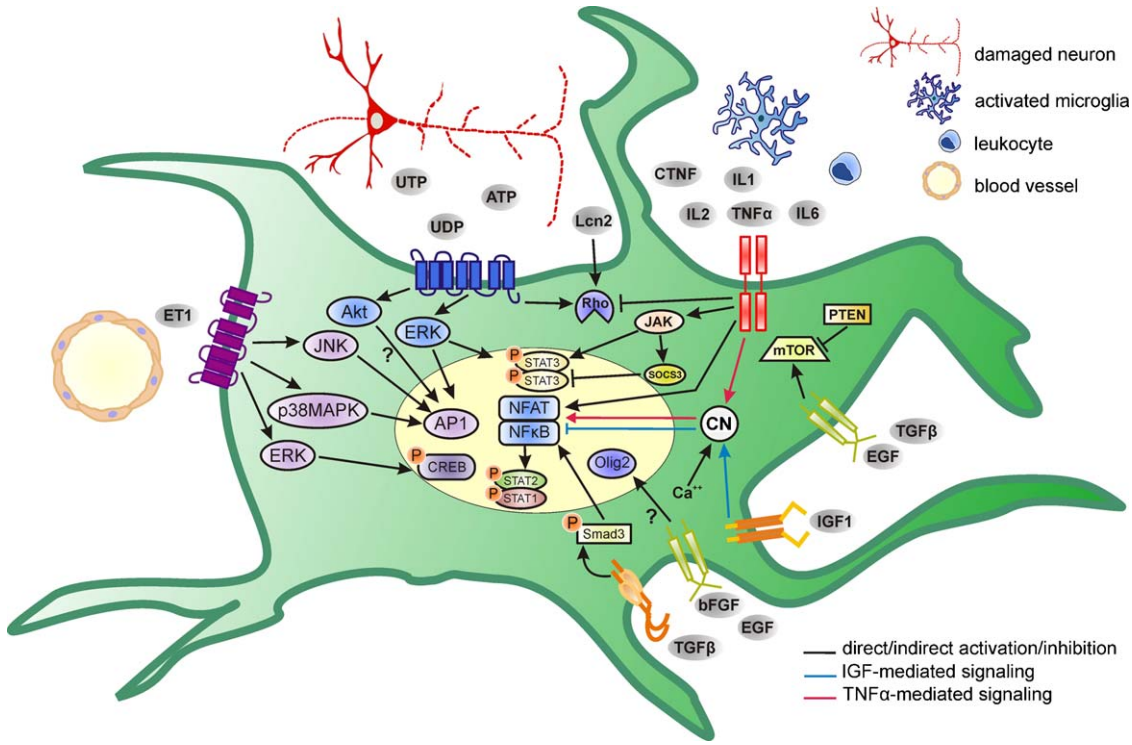

Fig. 2. Schematic drawing illustrating intracellular molecular cascades activated by astrogliosis triggers and elucidated in reactive astrocytes. Signals activating astrocytes are mainly released by activated microglia, infiltrating leukocytes, dying neurons and endothelial cells. However, astrocytes themselves take part in modulating their own reaction to injuries. Many intracellular mechanisms cooperate in astrocyte activation and involve both signaling converging at the nuclear level and pathways acting in the cytoplasmic compartment. Numerous cross-talks between different signaling pathways have been identified. Only pathways whose intracellular cascades have been elucidated in reactive astrocytes are included in the drawing (see text for further details). AP1, activator protein 1; bFGF, basic fibroblast growth factor; CN, calcineurin; CNTF, ciliary neurotrophic factor; CREB, cAMP response element binding; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; ET1, Endothelin 1; IFN, interferon; IGF1, insulin growth factor 1; IL, interleukins; JAK, Janus protein tyrosine kinases; JNK, c-jun N-terminal kinase; Lcn2, Lipocalin 2; mTOR, mammalian target of rapamycin; NFAT, nuclear factor activated T cells; NFkB, nuclear factor kappa B; p38MAPK, p38 mitogen-activated protein kinase; PTEN, phosphatase and tensin homolog; Smad, small mother against decapentaplegic; SOCS, suppressors of cytokine signaling; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TNF, tumor necrosis factor.

receptor family also activates inflammatory astrocytic pathways leading to cyclooxigenase-2 (COX-2) upregulation and release of arachidonic acid and its derivatives [19,22]. P2Y receptors can also modulate astrocytic cytoskeleton dynamics through a direct interaction with integrins [23], suggesting that nucleotides participate in astrocyte migration and chemotaxis (see Section 2.2 for details). However, the discrimination of the specific contribution of each P2Y family receptor to astrogliosis has been confounded by the lack of selective agonistic and antagonistic ligands.

While ionotropic P2X nucleotide receptors are mostly involved in the short-term cell-to-cell communication between neurons and astrocytes, or between astrocytes themselves [6], an important role in the long-term modulation of astrocytic functions has recently been demonstrated for the $P2X_7$ subtype. By increasing intracellular Ca^{2+} concentration, this receptor can modulate the synthesis of cytokines and inflammatory mediators, and also the expression of other purinoceptors [24], which in turn can promote reactive astrogliosis. Interestingly, this receptor is predominantly activated in conditions of pathological high extracellular ATP concentration, where it mediates the opening of a membrane "pore" that allows cytokine release and promotes cell death [25]. Thus, although the actual contribution of the $P2X_7$ receptor subtype to reactive astrogliosis is yet-to-be fully understood, this receptor might represent a useful therapeutic target to modulate astrocytic reaction.

Besides the predominant role played by nucleotides, reactive astrogliosis can be further enhanced by the activation of the nucleoside P1 G protein-coupled receptors (the A_1, A_{2A}, A_{2B} and A_3 subtypes; [26]), activated by adenosine (Ado). For example, both the A_{2A} and the A_3 subtypes were demonstrated to be involved in astrogliosis in vivo [27] and in vitro [28], respectively. Moreover, P1 receptors can also contribute to growth factor-mediated effects (see below). Since Ado is produced by the extracellular breakdown of ATP, its effects can become increasingly significant upon pathological conditions when high extracellular nucleotide concentrations are rapidly achieved (see above).

Finally, also guanosine can induce reactive astrogliosis [29], through a yet-to-be identified G protein-coupled receptor, further confirming the key role played by extracellular nucleosides and nucleotides in modulating brain tissue response after injury.

2.1.2. Cytokines and growth factors

Cytokines are the main inflammatory mediators constitutively expressed at low levels in the healthy adult brain, but released at high concentrations in response to injury or infections, thus contributing to both neurodegeneration and to astrocytic reactivity. In the injured brain, the major sources of cytokines are microglia cells, the brain resident immune cells. Similar to microglia and consistent with their contribution in the innate immune response of the brain, astrocytes themselves can release several pro-inflammatory cytokines, thus giving rise to an autocrine/paracrine loop of activation (Fig. 1b) [30].

In response to brain damage, several pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα), IL1β, and interferon γ (IFNγ) are released as primary mediators. They in turn lead to the production of secondary mediators, such as arachidonic acid metabolites (e.g., prostanoids), nitric oxide [31], and enzymes, including matrix metalloproteases (MMPs; [32], see also below).

Secondary mediators can further contribute to the long-lasting astrocytic response that is detected in chronic brain pathologies [22], thereby allowing inflammation to be spread outside the site of injury to the adjacent healthy areas, and to be sustained over time. Thus, inflammation is now recognized as a typical hallmark of both acute and chronic neurodegenerative diseases. It is activated as an initial reaction of the brain tissue to limit injury-associated tissue damage, but, when inappropriately sustained, inflammation can contribute to the development of an extensive secondary injury [31].

The astrocytic reaction is directly or indirectly induced by various pro-inflammatory cytokines (Fig. 2). A direct activation of astrocytes has been demonstrated in vivo for IL1β [33], TNFα [34] and IL6 [35] and in vitro for transforming growth factor – TGFβ1/2 – (for review, see [36]). Moreover, IL1, IL2, IFNγ, TNFα, TGFβ and others have been found to give rise to massive astrogliosis when injected directly into the brain or overexpressed in transgenic animals [37–39]. Similarly, ciliary neurotrophic factor (CNTF), a member of the IL6 family of cytokines with growth factor properties, can promote astrogliosis both in vitro [40] and after administration to the intact brain in vivo [41]. Some reactive traits together with progenitor features are also induced by the mitogen TGFα [42,43]. Conversely, a significant reduction of astrogliosis has been demonstrated with the blockade of several of the above-mentioned mediators [33,35,44,45]. Yet, some other cytokines such as IL10, IFNβ and Epo, secreted after lesion by diverse cellular elements including astrocytes, are known to attenuate gliosis [7–9].

Other major regulators of the nervous tissue response to damage are GFs. Upon lesion, these mediators are secreted by activated microglia, and by astrocytes themselves, in accordance with their trophic and supportive role for neurons in the intact brain [46]. Indeed, astroglia upregulates the expression of an enormous array of GFs (Fig. 1a and b), including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF; [47]), neurotrophin 3 (NT3; [48]), CNTF (see above), vascular endothelial growth factor (VEGF; [49]), epidermal growth factor (EGF; [50]), basic fibroblast growth factor (bFGF; [51,52]), insulin growth factor 1 (IGF1; [53]) and glial cell-line derived neurotrophic factor (GDNF; [54]). GFs play a key role in pathological conditions, when they trophically support damaged neurons, oligodendrocytes, and, in some instances, activated progenitor cells (see Section 3.2). In addition, they also act on astrocytes in an autocrine/paracrine fashion, thus contributing to a feed-forward amplification loop, which starts and sustains reactive astrogliosis (Fig. 1b). For example, the typical features of reactive astrocytes (i.e., cell proliferation, increased GFAP expression, and emission of long and branched processes) have been observed after exposure to bFGF [18,55], EGF [56,57], IGF1 [58], and CNTF (see above). Moreover, the in vivo administration by chronic minipump infusion of neutralizing antibodies against the VEGF receptor-1 significantly reduced the extent of reactive astrogliosis, thus indicating that VEGF is controlling astrocyte response to injury [59].

It is important to point out that the various regulatory molecules do not act on astrocytes independently, not only because activated astrocytes can in turn synthesize and release a wide array of mediators that take part in reactive astrogliosis (see above), but also because they interfere at the level of intracellular biochemical pathways. For example, ATP and bFGF synergistically induce the typical features of reactive astrogliosis in striatal astrocytes [18,60]. Moreover, the A_{2A} receptor antagonist SCH58261 prevents bFGF-induced astrocytic stellation, thus suggesting that the effects of GFs are to some extent mediated by the purinergic system [55]. Indeed, a regulatory connection between inflammatory cytokines, Ado and its receptors has been demonstrated in astrocytes grown in vitro. For example, exposure to the astrogliosis-promoting agent TNFα reduced the internalization and down-regulation of the A2B receptor subtype [61].

Furthermore, growing lines of evidence suggest that GF receptors (i.e., bFGF, EGF and NGF receptors) can be transactivated by P2Y receptor activation. This can be achieved by the P2Y-mediated activation of soluble kinases, which in turn phosphorylate GF receptors, or of MMPs, which degrade extracellular matrix components and cut membrane-bound GF precursors to active GFs, or even through the coupling to integrin-specific pathways (see also above) [60].

Other cooperative effects have been shown for cytokines. For instance, although not effective per se, both IL6 and CNTF significantly promote EGF-mediated astrocyte proliferation [62]. Similarly, EGF and TGFβ1 synergistically increase the astrocytic production of chondroitinsulphate proteoglycans (CSPGs), abundant components of the glial scar [63]. Also some transcription factors (e.g., nuclear factor of activated T cell, NFAT) might represent the common pathway underlying the effect of cytokines and other mediators of astrogliosis, such as nucleotides (see Section 2.2).

Thus, the astrocytic response to brain damage is controlled by an integrated network of signaling systems that allow the fine-tuning of reactive astrogliosis.

2.1.3. Other signals

Other signals have recently been implied in astrocyte reactivity. Interestingly, some of them are secreted and act in autocrine loops, further underlining that astrogliosis is a self-regulated phenomenon. Other factors are instead related to changes in contact-mediated signals, which thus appear to be additional regulator of the astroglial functional state.

Lipocalin 2 (lcn2) is a member of the lipocalin family that binds and transports small hydrophobic molecules [64]. Astrocytes both secrete and respond to lcn2 (Fig. 2), whose production increases after inflammatory stimulation in vitro [65]. Lcn2 induces an enhanced sensitivity to cytotoxic stimuli, GFAP upregulation, cell migration, and the acquisition of a reactive phenotype [65]. Another secreted mediator of astrogliosis is Endothelin 1 (ET1) (Fig. 2), a potent vasoconstrictor peptide produced by endothelial cells in the healthy brain. Upon injury, reactive astrocytes become the major source of ET1 and also upregulate type B ET receptors (ET-Rs) [66]. A direct role for ET1 in reactive gliosis was demonstrated both in vitro and in vivo by infusion of exogenous ETs or ET-R agonists, which cause astrocyte hypertrophy, cytoskeletal changes, proliferation, neurotrophin production, and modulation of metabolic properties. Conversely, injection of ET-R antagonists inhibits reactive gliosis (see Ref. [67] and references therein). In addition, ET1 promotes the production of both secreted MMPs and their inhibitors that regulate remodeling of the extracellular matrix [68].

During tissue reaction to injury, changes also occur in the astrocyte interaction with the extracellular molecular and cellular milieu, that in turn feedback on the astrocyte state. For instance, disruption of the contact between astrocyte endfeets and vascular basement membranes by astroglia specific deletion of integrin β1, triggers a partial reactive state, including hypertrophy, GFAP, vimentin and Tenascin-C upregulation but excluding proliferation [69]. Other contact-related regulators of astrogliosis are Ephrins (Ephs) and their receptors [70]. These molecules are physiologically expressed in the CNS but become upregulated following injury in astrocytes possibly by inflammatory cytokines [70,71]. Genetic deletion of Eph4A from astrocytes impairs their proliferative response to cytokines, GFAP upregulation and glial scar formation [70,71], indicating that Eph receptors are directly involved in the initiation of reactive gliosis and in the scarring process (see also below).

2.2. Intracellular transduction pathways and cellular reactivity

The molecular mechanisms translating injury-derived signals into astroglia reactivity are numerous and their intracellular interactions are in large unclear. Some of the morphological and functional changes seen in reactive astrocytes appear regulated exclusively at the cytoplasmic level. Conversely, other aspects of astroglia reactivity implicate the activation of intracellular cascades leading to nuclear responses and dramatic gene expression changes.

With respect to signal transductors mostly active at the cytoplasmic level, GFs have recently proved to activate the mammalian target of rapamycin kinase (mTOR) in reactive astrocytes (Fig. 2). Indeed, treatment with the mTOR-selective antagonist rapamycin prevents proliferation, migration and intermediate filament upregulation in EGF-activated astrocytes [57], and deletion of the mTOR negative regulator phosphatase tensin homolog (PTEN) promotes astrocyte hypertrophy and proliferation (Fig. 2) [72]. Although mTOR effects in astrogliosis are consistent with its known action as cytoplasmic modulator of protein translation and cytoskeletal dynamics [73], indirect actions mediated by transcriptional events cannot be excluded.

The Rho family of small GTPases represents other cytoplasmic players (Fig. 2). These molecules mediate the convergence of both extracellular and intracellular signals onto the cytoskeleton, resulting in morphological plasticity [28,74]. Indeed, the Rho GTPase Cdc42 is required after scratch wound for early astrocyte polarization and, upon activation by integrins, sustains oriented migration [75]. Likewise, the Rho GTPase family mediates astrocyte migration upon interaction of integrins and P2Y receptors (mainly the $P2Y_2$ receptor subtype; [23]) and lcn2 stimulation (Fig. 2) [65]. On the contrary, other injury-related factors, such as pro-inflammatory cytokines, inhibit the Rho/ROCK pathway (Fig. 2), resulting in impaired astrocyte migration [76] accompanied by morphological stellation, indicative of a reactive state [76,77]. Thus, GTPases may independently regulate distinct morphological/functional changes in astrocytes.

Most of the injury-related signals converge on a limited number of intracellular molecular cascades capable of conveying information to the cell nucleus. Mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) phosphorylation mediates the effects of extracellular nucleotides, GFs, and endothelin (Fig. 2) [22,67,78–80] via increased activation and/or synthesis of several transcription regulators such as CREB and the AP1 complex components c-Jun and c-Fos (Fig. 2) [18,67,78]. These transcription factors drive GFAP upregulation and cell proliferation [22,78–80]. The PKB/Akt system converges on the same nuclear complex (Fig. 2). It has been reported that this system is activated by P2Y-mediated signaling, resulting in astrocyte proliferation and anti-apoptotic effects [81]. Upon P2Y-mediated signals, MAPKs also activate the signal transducer and activator of transcription (STAT) pathway, leading to modulation of gene expression (Fig. 2) [61]. A similar convergence on STAT transducers is operated by the Janus family kinases (JAK) in response to extracellular GFs and cytokines including the astrogliosis triggers IL6, CNTF, EGF, and TGFα (Fig. 2) [82]. STAT3 activation in astrocytes was indeed reported in vivo after focal cerebral ischemia [83], denervation [84] as well as in enthorinal cortex lesion [85]. In line with a crucial role of STAT molecules in orchestrating astroglia reactivity, their genetic deletion or inactivation strongly reduces specific aspects of reactive gliosis, such as astrocyte proliferation, migration and glial scar formation [86,87]. Notably, JAK-STAT activation by cytokines also induces a delayed activation of suppressor cytokine signaling molecules (SOCS; Fig. 2) [88], as demonstrated in vivo in astrocytes upon ischemia [89]. Interestingly, SOCS operate as negative feedback regulators of the JAK–STAT pathway [90], thus contributing to the modulation of astroglia reactivity. Indeed, genetic ablation of SOCS3 results in increased astroglia migration to seclude the damaged area (see below), which is instead sustained by STAT activity [86]. Thus, ongoing astroglia reactivity appears modulated by antagonistic mechanisms that may alternatively prevail at distinct phases of the astrocyte response to lesion.

The basic helix loop helix (bHLH) repressor Olig2 has also been recently involved in astrogliosis (Fig. 2). It is expressed by reactive astrocytes in different injury models [91,92] and its translocation from the nucleus to the cytoplasm in proliferating glial progenitors has been suggested to mediate differentiation into reactive astrocytes [93,94]. Further, genetic Olig2 deletion in astrocytes reduces reactive astrocyte proliferation [95]. No data are currently available on injury-related signals involved in Olig2 induction in astrocytes. However, studies on progenitor cells [96] indicate GFs within the lesion (i.e., bFGF or EGF) as potential Olig2 triggers (Fig. 2). On the whole, in astrogliosis Olig2 appears critical in the expansion of the reactive astrocyte pool and in the subsequent maturation of the reactive traits.

Amongst nuclear transducers, the nuclear factor kappa B (NFkB) family of transcription factors mediates cytokines-activated signals (Fig. 2). Pro-inflammatory cytokines trigger NFkB nuclear translocation and transcriptional functions by activating complex kinase cascades (for review, see [97]). In turn, NFkB promotes the production of chemokines and inflammatory molecules such as TGFβ, partly cooperating with the STAT pathway (Fig. 2) and thereby influencing lymphocytes recruitment [98,99]. It is also directly involved in the deposition of CSPGs [98].

In reactive astrocytes, NFkB nuclear signaling and its related transcription factor NFAT are also targets of the phosphatase calcineurin (Fig. 2), which can be activated by both purines/pyrimidines and pro-inflammatory cytokines (TNFα and IL1β) [100–102], thus possibly representing their common downstream pathway. Acutely activated calcineurin promotes NFkB and NFAT nuclear translocation, resulting in the release of inflammatory mediators [100–102]. The importance of this pathway is shown by the reduction of astrocytic pro-inflammatory activity upon calcineurin blockade by immunosuppressive drugs [103]. Conversely, at late stages after damage, GFs such as IGF1 and other mediators such as superoxide dysmutase (SOD) further enhance calcineurin activation (Fig. 2), switching its function towards inhibition of the above-mentioned inflammatory cascade [100]. Thus, calcineurin mediates opposite effects in reactive astrocytes, depending on the activating factors and the cellular context.

In summary, damage-related factors induce the activation of several intracellular pathways that control reactive astrocytic features. While some intracellular transductors (i.e., Rho GTPases, JAK–STAT, Olig2 and MAPK/ERK) are mostly involved in the control of motility-related aspects of astrogliosis, such as migration and cell proliferation, NFkB and NFAT appear instead specifically implicated in the regulation of astroglia inflammatory activity. In addition, the astrocytic transduction machineries partly target the same astrogliotic features, thereby operating in a redundant fashion, or perform opposite functions, depending on the cellular context, activating factors and gliosis phases.

3. The double-edged sword: astrogliosis in acute and chronic damage

Astrocyte responses to injury are aimed at both protecting the nervous system, and at sealing off the damaged area, leaving the heavily injured zone to its natural degenerative fate, while preserving the less affected tissue. Once activated, these responses seem to proceed in a quite stereotyped way, independently of the initial source of injury. Hence, they may lead to predominant reparative or destructive outcomes depending on the context in

which they occur, for example the extent and type of injury (i.e., chronic vs. acute), and time point after damage.

In the following section we will dissect out some of the cellular/molecular mechanisms supporting detrimental or beneficial features of astrogliosis in an attempt to understand how these opposing functions can be reconciled.

3.1. Restriction of plasticity and amplification of cell damage

The healing response to injuries of the mature CNS culminates in the formation of a tight barrier, the glial scar, which consists predominantly of reactive astrocytes (Fig. 1e). Scarring astrocytes have long been considered as a major impediment to regeneration of damaged axons [104–106], and reactive gliosis regarded as detrimental to nervous tissue repair and functional restoration. This notion was further consolidated by the discovery that the scar tissue is highly enriched with molecules inhibitory to axon regeneration and remodeling such as CSPGs, Eph receptors and their ligands, Slit proteins, Semaphorins and Tenascin R [4]. CSPGs produced after injury originate from reactive astrocytes responding to GFs and pro-inflammatory cytokines (see Section 2), halt axon regeneration (for review, see [107]) and induce the formation of dystrophic growth cones [4]. An analogous negative role on axonal growth has been shown for scar Ephs, namely EphA4, whose deletion, besides attenuating reactive gliosis and scar formation, allows axon growth and functional improvement in injured animals [70]. Similarly, the expression of Slit modulators of axon guidance increases in reactive astrocytes [108] and may contribute to regeneration failure. Finally, other scar inhibitory elements such as Semaphorin 3A, produced by meningeal fibroblasts reacting to damage [109], and the cell adhesion molecule Tenascin R, upregulated and secreted by astrocytes after lesion, may act as barriers to tissue recovery [110,111]. Furthermore, upregulation of intermediated filaments (namely GFAP and vimentin) has a key role in the development of some of the long-term inhibitory features of astrogliosis. In fact, the attenuation of reactive gliosis observed in mutant mice deficient for GFAP and vimentin correlates with improved integration of neural grafts and enhanced posttraumatic regeneration [1]. However, as illustrated below (Section 3.2), intermediate filament induction instead has a positive role shortly after damage, where it helps reduce the toxic effects of extracellular glutamate and allows barrier reconstruction [111].

Although astrocytes continue and even intensify their trophic activities upon injury (Fig. 1a; see Section 3.2), in the condition of extremely severe or prolonged damage such as in the core of ischemic insults, their energetic metabolism may succumb and essential functions, such as the activity of Na^+/K^+ ATPase regulating membrane potential, may be lost. The ensuing depolarization of astrocyte membrane, together with an increased extracellular Na^+ concentration, can reverse glutamate transport, produce glutamate efflux and transform astrocytes into a source of substances toxic to neurons. Nevertheless, these events are thought to normally occur at a time when neuronal damage is already beyond repair, implicating that they have a limited impact on secondary death [112]. Glutamate, however, may also be released by reactive and fully functional astrocytes through their hemichannels, which can be opened by lowering extracellular Ca^{2+} concentration, acidosis, or even through $P2X_7$ receptors activated by excessively high extracellular ATP. All these events occur during lesions such as ischemia, and may account for the spreading of death signals (for review, see [112]). Damage diffusion may also occur via astrocytic gap junctions, although this form of cell-to-cell communication is globally reduced upon damage [113].

A series of studies further revealed that the secretory activity of reactive astrocytes can exacerbate tissue lesion (Fig. 1b). For instance, released pro-inflammatory cytokines such as TNFα can inhibit neurite growth and kill oligodendrocytes [114,115]. Similarly, reactive astrocytes can produce and release arachidonic acid metabolites, nitric oxide and reactive oxygen species [31], which may enhance neuronal degeneration and axon demyelination by promoting inflammation [5,116]. In this regard, myelin degradation can be favored by reactive astrocyte-mediated extravasation of pathogenic auto-specific T cells, which can attack myelin sheaths. This detrimental function is mediated by surface expression of the cell-adhesion molecule VCAM1, which facilitates T cell migration into the CNS parenchyma, the secretion of chemotactic molecules, and the release of MMPs (Fig. 1b). These enzymes degrade a variety of extracellular matrix components and tight junctions between endothelial cells, leading to disruption of the blood–brain barrier (BBB) and infiltration of immune cellular elements [32]. Suppression of MMPs activity reduces immune cell trafficking into the CNS and attenuates experimental autoimmune encephalomyelitis [118]. In parallel, some features of reactive astrocytes are known to hinder remyelination from oligodendrocyte progenitors. Indeed, astrocyte Semaphorins block oligodendrocyte progenitor recruitment [117] and the increased secretion of bone morphogenetic proteins (BMPs) by reactive astroglia can inhibit oligodendrocyte progenitor differentiation [119].

MMP activity has proved detrimental also in other injury conditions such as ischemia or trauma [32] where soon after insult it triggers the amplification of secondary cell damage and the promotion of inhibitory scarring [120]. However, at later stages after injury, MMP activity instead favors tissue remodeling, white matter sparing and functional recovery as shown by worsening of the injury outcome by their delayed inhibition [120,121].

Some of the major negative traits of reactive astrocytes, such as CSPG secretion, and production of inflammatory molecules, can be reduced by NFkB inhibition. In line with this, in vivo antagonization of this pathway in astrocytes promotes neuronal resistance to injury and remodeling of spared axons [98,120]. Likewise, a recent study showed that the delivery in vivo of an irreversible inhibitor of EGFR promotes structural and functional recovery from spinal cord contusion [122]. Since EGF receptor activation triggers astrocyte reactivity [56] and EGFR ligands stimulate the secretion of CSPGs [63] contributing to astrocyte scarring [123,124], astrocytic changes are supposed to underlie the positive outcomes of such manipulations.

3.2. Protective/trophic response

The concept of a protective role for astroglial reactivity has only recently been established, emerging from the ability of reactive astrocytes to isolate the damaged core of vascular and traumatic lesions from the surrounding healthy tissue, thus reducing the spreading of toxic substances and metabolites released from dead cells and limiting the development of secondary damage [125]. These beneficial effects are related to the capability of astrocytes to produce signals supportive for neuronal and oligodendroglial survival, to preserve and restore altered homeostatic conditions, and, when lost, to re-establish the anatomical barriers (glia limitans and BBB) necessary for the correct CNS functioning (Figs. 1 and 3).

Astrocyte protective actions are exerted by scavenging extracellular glutamate, storing energy, supplying neighbouring cells with energetic compounds, and neutralizing toxic substances (Fig. 3). For instance, one of the major causes of secondary damage in case of ischemia or trauma is the massive release of glutamate (due to direct cell injury or neuronal dysfunction) that triggers secondary excitotoxic events in neurons. Astrocytes are crucial regulators of glutamatergic signaling in normal nervous tissue function by active removal of extracellular glutamate operated by

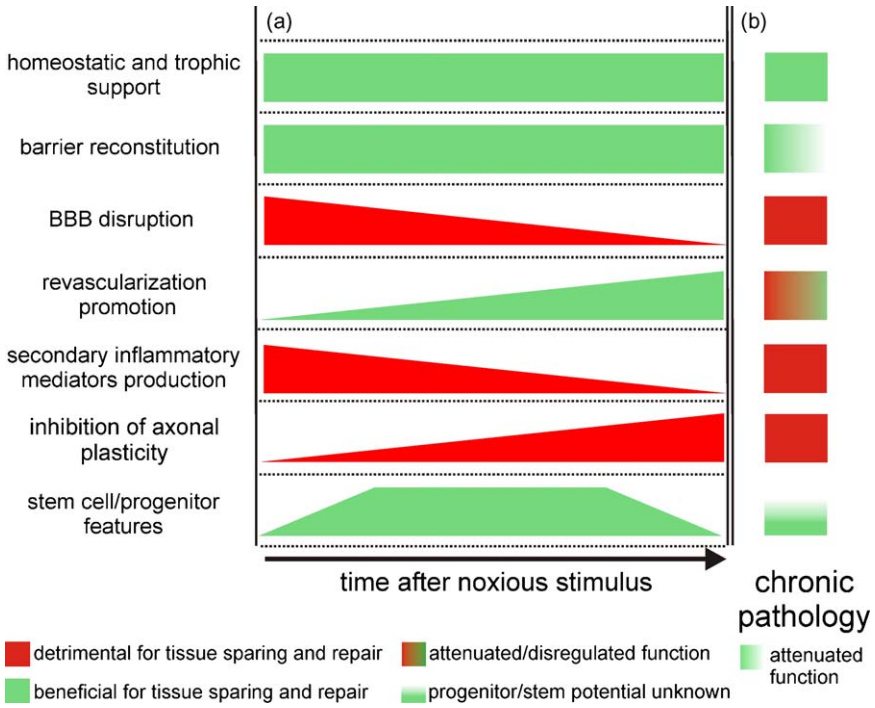

Fig. 3. Astrocyte functions in acute and chronic lesions. Panel (a) illustrates the evolution of detrimental and beneficial effects of astrocytic functions over time after acute injury. Increases or decreases over time of each function are represented as variation in the thickness of the horizontal bars. Panel (b) summarizes the outcomes of the same functions in chronic neurodegenerative situations. BBB, blood–brain barrier.

the Na^+-dependent glutamate transporter 1 (GLT1) and the glutamate/aspartate transporter (GLAST) [126]. Importantly, astroglia glutamate removal continues upon injury [127] and strongly contributes to tissue protection as shown by dramatic damage exacerbation in the case of transporter knock-down [128]. In vitro studies also indicate that injury mediators such as EGF, bFGF, IGF1 and CNTF, as well as GFAP upregulation can potentiate glutamate scavenging by inducing GLT1 and GLAST upregulation or transporter membrane redistribution [111,129].

Independent of transporter expression, astrocyte glutamate uptake is strictly conditioned by the availability of ATP. Yet, by enabling glutamine synthase (GS) to convert glutamate to glutamine, ATP preserves a favorable glutamate gradient allowing its uptake into astrocytes [130]. GS levels are increased by the injury-released signals FGF and NGF, revealing a potential enhancement of the scavenging capability of reactive astroglia [131]. ATP is also essential for the function of the Na^+/K^+ ATPase, whose action crucially maintains the ionic membrane gradient and avoids astroglia transporters running backward to release glutamate when the Na^+ gradient is inverted. When the energy substrates glucose and oxygen are lost (i.e., in ischemia), the persistence of this function in astrocytes is to some extent granted due to the capacity of astroglia to maintain high energy levels upon lesion and to utilize diverse energy sources. For example, astrocytes convert stored glycogen to glucose or lactate to obtain energetic substrates, thereby sustaining their own metabolisms or possibly passing these substrates to neighbouring neurons for energy production [132]. Moreover, CNTF-activated astrocytes also increase fatty acid beta-oxidation and ketolysis to produce energy, while decreasing glycolytic pathways [40]. This metabolic plasticity confers a remarkable ability to resist to metabolic insults and support the survival of surrounding neurons [40].

Furthermore, the enhanced capability to metabolize fatty acids also has a detoxificant function when potentially toxic free fatty acids are released from phospholipids in the plasma membrane in several lesion conditions [133]. The implementation of detoxifying actions after damage is also indicated by the increased levels of the antioxidant glutathione pathway, which is potentiated by exposure to CNTF, IL1β and TNFα [134], and whose molecular components are made available to neurons for their own antioxidant defence [135]. Thus, several traits of astrocyte activation appear as adaptive responses to counteract the shortage of energy supply and limit accumulation of otherwise toxic metabolites in the damaged nervous tissue.

Other beneficial aspects of astrocyte reactivity are related to their participation in tissue remodeling after injury (Fig. 3). VEGF is produced by reactive astrocytes after traumatic injury [136], inflammatory lesions, and hypoxic conditions ([137] and references therein). This growth factor, in addition of being directly neuroprotective [136], strongly promotes angiogenesis [138], consistent with a role for reactive astrocytes in neovascularization after lesion. However, VEGF also acts a BBB disaggregation signal via downregulation of endothelial tight junction components [137]. In specific pathological conditions such as CNS inflammatory disorders, this pathway may exacerbate tissue damage by sustaining inflammation and leukocyte infiltration instead of supporting repair.

The restoration of the glia limitans and BBB is necessary to re-establish CNS homeostasis and proper function after nervous tissue disruption. If these processes are not fulfilled after lesion, damage to the nervous tissue is amplified by increased immune cell infiltration, neuronal death and demyelination [86,139,140]. Crucial to barrier reconstitution are reactive astrocyte proliferation and migration, as shown by conditional ablation of reactive astrocytes or selective blockade of defined intracellular signaling pathways [86,139,140]. Interestingly, in addition to STAT/Olig2 activity (see Section 2.2), GFAP upregulation is required for proper scarring response [111]. Other factors implicated in astroglial migration and wound closure are Smad-3-mediated TGF signaling [141] and acquaporins (AQPs), which facilitate reactive astroglial movements by controlling water fluxes [142]. Further, the cross-talk between Ephs and their receptor at the reactive astrocyte–

meningeal fibroblast interface consolidates the formation of the new glia limitans by deposition of new basal lamina [71], whereas direct contact of astrocytes with endothelial walls or local diffusion of astrocyte-derived factors (TGFβ, GDNF, bFGF, angiopoietin 1) likely participate in inducing BBB-forming phenotypes in endothelial cells [143]. Also the purinergic system contributes to promote beneficial properties in reactive astrocytes by stimulating matrix changes favorable to axonal sprouting and remodeling upon $P2Y_4$ activation and stabilizing cell-to-cell contact between astrocytes when A_3 adenosine and P2X/P2Y receptors are stimulated [144].

Finally, the wide set of GFs upregulated by astrocytes in lesion conditions (see Section 2) provide direct trophic support to neurons and oligodendrocytes to limit secondary damage. Moreover, some of these factors together with other signals (i.e., IL6) to some extent create a permissive environment for remyelination by their action on oligodendrocyte precursor migration, oligodendrocyte proliferation, and differentiation (for review, see [116]). In summary, the long-standing concept of astrogliosis as an obstacle to brain repair has now greatly evolved with the discoveries of the many and essential beneficial effects of astrocyte reactivity for damage limitation and tissue preservation. It is also increasingly clear that the inhibitory components of the scar undergo extensive remodeling over time so that the scar becomes progressively more permissive to axon growth [145]. Moreover, at distinct times post-injury the same signals or molecular players (i.e., VEGF, MMPs, intermediate filaments, but also inflammatory molecules) can operate either negative or positive actions with respect to damage extent and functional repair [1,32,136]. In most cases, however, their crucial contribution to tissue preservation or remodeling renders them globally beneficial; only in cases of chronic pathologies some effects may become overtly maladaptive (Fig. 3), as occurs in multiple sclerosis when inflammatory mechanisms are exacerbated. On the whole, this more comprehensive view of astrogliosis offers new basis to better understand how its healing potential can be implemented towards fully adaptive responses.

4. Reparative potential of parenchymal glia

New perspectives on the reparative potential of astroglial cells derive from the discovery that the astroglia lineage hosts neural stem cells generating neurons and glia in the mammalian brain [146]. This lineage includes radial glia during development [147] and astroglia subsets of the germinative areas (the subependymal layer of the lateral wall of the lateral ventricles, and the subgranular layer of the hippocampus) of the mature brain [148,149]. The observation that the same lineage also directly leads to parenchymal astroglia [150] suggests that parenchymal and germinal astrocytes may share common features, in spite of the fact that the former do not normally exhibit stem cell properties or multipotency.

Many molecular, structural and functional similarities between radial glia, parenchymal astrocytes and germinative neural stem cells have been identified and extensively revised (for reviews, see [46,151]). Briefly, radial glia, parenchymal astroglia progenitors and germinative astrocytes share a variety of molecular traits (i.e., GFAP and brain lipid binding protein, blbp, gene promoter activity, expression of vimentin, nestin, S100β, GLAST, GLT1, Tenascin C and the RC1 and RC2 intermediate filament epitopes) and ultrastructural features (glycogen granules). They also all show K^+ conductance at rest, and exhibit hemi-channels, connexin 43-mediated coupling, and $GABA_A$ receptors, while they do not express AMPA channels (absent in most mature astrocytes). Functionally, radial glia, astroglia progenitors and germinative astrocytes display proliferation, although at different extents, and give rise to progenies including all the three neural lineages (neurons, oligodendrocytes, astrocytes). Furthermore, they all display the two "key-features of stem cells", namely, self-renewal and multipotency, demonstrated in vitro with the neurosphere assay [46]. Remarkably, postnatal immature astrocytes respond to neurogenic transcription factors active both during development and in adult germinative areas by adopting a neuronal fate [152].

However, during maturation, parenchymal astrocytes cease proliferation and lose multipotency together with the capability to reveal stem cell-like properties in vitro [2,153]. In addition, they also downregulate several immature/stem cell state molecular markers (e.g., nestin, RC1/2, vimentin, blbp, Tenascin C), and specifically start expressing defined K^+ conductances, considered as a hallmark of astrocyte differentiation and cell cycle exit [46,151]. Notably, during their reaction to damage, quiescent astrocytes change their phenotype, and reveal many of the molecular traits of earlier progenitors and stem cells [2,46,151], suggesting a dedifferentiation process or the transition towards a germinative state. Consistently, subsets of quiescent astrocytes also resume proliferation after damage and, although remaining within their lineage in vivo, reveal a capacity for self-renewal and multipotency in vitro in the neurosphere assay [2]. In line with a broadening of plastic properties in activated glia, neurogenic attempts can be evoked in proliferating glia reacting to injuries by viral-mediated overexpression of neurogenic instructors or by antagonising anti-neurogenic determinants [91,154]. Moreover, spontaneous glial plastic changes indicative of pluripotency have been recently documented after lesion [94,155]. On the whole, evidence is accumulating that during the reaction to injury glial cells undergo modifications leading to the (re)acquisition of some progenitor/stem cell functions.

Importantly, this process may also allow the implementation of the immature astrocyte capability to activate healing modalities fully beneficial for tissue repair, which is a typical trait of the immature gliotic response [1,4]. However, in the adult nervous tissue strong signals operate that hamper the (re)acquisition of progenitor/stem cell potentialities, as well as their expression, while fostering specific astrogliosis traits detrimental for circuit remodeling or neurogenesis [1,2,6]. Thus, the neutralization of restrictive factors and/or the enhancement of supportive signals may potentiate the recapitulation of stem/developmental capabilities, possibly also allowing neuronal replacement, and ultimately may favor reparative astroglial responses to damage.

5. Potential molecular targets to implement brain self-repair

Astrogliosis in CNS injury is a dynamic process evolving through different stages, whose effects may vary depending on the damage extent and injury type (Fig. 3). Its crucial involvement in determining the degree of brain pathology and of neurological damage, together with its universal participation in tissue response to noxious stimuli, render astrogliosis an appealing target for therapeutic interventions aimed at promoting nervous tissue preservation and repair. However, as highlighted in the previous sections, its molecular regulators are myriad, closely intermingled and often modulating both beneficial and detrimental effects. Hence, to date, there appears to be no single molecular target, which can be manipulated to promote the beneficial healing effects in all injury conditions. Yet, two general criteria can be envisaged to define approaches able to orient astrogliosis towards positive outcomes. First, the evaluation of the effects of defined gliosis mediators and functions (see Section 3, Fig. 3) at different stages after damage or in different lesion conditions can offer a key to identify molecular targets whose manipulation at specific time points may foster neuroprotection or regenerative events. Alternatively, instead of focusing on individual aspects of gliosis, the modulation of factor(s) leading to a

Table 1
Possible pharmacological approaches to modulate reactive astrogliosis signaling pathways and their functional outcome.

Signal	Agonist	Antagonist	Effects	References
Adenine nucleotides	ATP αβmeATP		↑ proliferation of astrocytes ↑ gliosis	[18,20,22][a]
	ADPβS		↑ gliosis	[21]
	bzATP ($P2X_7$ receptor subtype)		↑ cytokine release ↑ Akt and ERK1/2 activation	[24][a]
Adenosine	Cl-IB-MECA (A_3 receptor subtype)		↑ gliosis	[28][a]
		SCH58261 (A_{2A} receptor subtype)	↓ bFGF-mediated gliosis	[55][a]
Calcineurin		Cyclosporine A (CsA)	↓ neuroprotection	[167]
		FK506	↓ inflammation	[103]
CSPG		ChABC	↑ axonal plasticity ↓ glial scar formation	[107]
EGF/TGFβ		PD168393; AG1478 (EGFR TK inhibitor)	↑ neuroprotection ↑ functional recovery	[56,123]
Epo	rhEpo		↑ functional recovery ↑ neuroprotection	[7]
IGF1		Picropodophyllin (PPP)	↓ neuroprotection	[167]
MMPs		FN439; BB1101; BB94 (broad-spectrum MMPs inhibitors)	↓ BBB distruption ↓ hemorrhage ↓ VEGF	[32,119]
Notch		DBZ ((S,S)-2-[2-(3,5-difluorophenyl) acetylamino]-N-(5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl)propionamide)	↓ cell damage	[166]
		DAPT (N-[N-(3,5-difluorophenacetyl-L-alanyl)] -S-phenylglycine t-butyl ester)	↑ functional recovery	
p38MAPK	MW01-2-069A-SRM		↑ functional recovery	[156]
Shh	Hh Agonist 1.6		↑ glial plasticity	[168]
		Ciclopamine	↓ glial plasticity	[160]
TGFα	rhTGFα		↑ axonal growth ↑ glial plasticity	[159]
Uracil nucleotides	UTP ($P2Y_2$ receptor subtype)		↑ astrocyte migration	[23][a]
VEGF	VEGF-A		↑ BBB distruption	[137]

[a] Modulation of gliosis has been evaluated in vitro.

broadening of parenchymal astroglia plasticity and to the (re)acquisition of immature/stem cell properties and functions may eventually unfold and coordinate multiple and distinct features of astroglia reactivity towards better healing responses.

Globally, reactive gliosis appears to play an essential role for damage seclusion in the first stages after CNS injury, while it seems to pose an obstacle to regeneration and recovery at later steps or in chronic situations (Fig. 3) (see Section 3). Amongst the time-specific signals which could possibly be targeted to promote repair, early MMPs or VEGF are interesting, as the activities of these proteins early in pathology result in BBB breakdown with consequent exacerbation of tissue damage (Fig. 3) [32,136,137]. Therefore, their blockade may turn out to be beneficial in some injury conditions such as stroke, by limiting secondary damage [32], chronic inflammation, and by reducing the infiltration of immune cells through the disrupted BBB [137]. In these diseases, also the persistence of a chronic inflammatory state in reactive astrocytes can be highly detrimental due to the continuous production of toxic molecules and persistent secretion of cytokines. To attenuate these negative effects, new approaches have been recently proposed, in addition to more conventional anti-inflammatory treatments (i.e., steroid-based or non-steroidal drugs; see [35]). Infact, genetic inactivation of the transcription regulator NFkB in reactive astrocytes diminishes inflammation, CSPG deposition and myelin loss upon spinal cord injury [98]. Contextually, it can promote axon sparing and sprouting [122] in correlation with improved locomotion [98]. Furthermore, specific inhibitors of the cytoplasmic transducer p38/MAPK (Table 1) have been shown to decrease the prolonged production of inflammatory cytokines by activated glia in a mouse model of chronic neurodegeneration, resulting in neuroprotection and behavioral improvement after lesion [156]. Amongst secreted modulators of astrogliosis, the anti-inflammatory cytokine IL10 has proved to confer resistance to ischemic insults by reduced cytokine production and oxidative stress regulation [8]. Likewise, IFNβ and Epo treatments attenuate astrogliosis and promote functional recovery after injury [7,157]. In particular, besides its general anti-apoptotic and tissue-protective properties, Epo specifically attenuates CSPG deposition, while implementing potentially beneficial functions of astrogliosis such as promotion of vascularization and AQP-mediated edema resolution [7,158]. Similarly, the enhancement of a sustained or delayed activation of the calcineurin pathway (either by IGF1 or pharmacological manipulations; Table 1) may mediate a protective phenotype of astrocytes. Conversely, the antagonization of its early activation by pro-inflammatory cytokines may limit the ensuing pro-inflammatory deleterious effects [100]. Given the anti-inflammatory properties of IGF1, this signal may be an important factor to implement to obtain effective healing in several injury conditions [100]. Despite the results of the above-mentioned manipulations (i.e., anti-inflammatory cytokines, NFkB; see also Table 1) appear encouraging overall, further studies aimed at their therapeutic applications may be slowed down by the actual lack of specific pharmacological tools that could be translated into useful drugs.

Other approaches to promote beneficial astrogliosis may exploit the removal of axon growth inhibitors accumulated with

scarring at later time points after lesion (Fig. 3). Inhibitory CSPGs can be eliminated in situ by enzymatic digestion of glycosaminoglycan side chains by the bacterial enzyme chondroitinase ABC [107], by modulating the signals that promote their production in astrocytes (i.e., cytokines and GFs; [63,107]), or by the enhanced activation of enzymes sustaining long-term adaptive changes, such as specific MMPs. However, any treatment interfering with scar formation and extracellular component deposition has to bypass or preserve the acute gliotic response, given the protective role of the early astrocyte activation for sealing and cleaning the injury site, and restoring homeostasis (see also [125]).

Also the purinergic system could represent an interesting therapeutic target, provided that the sequential involvement of the various receptor subtypes in modulating astrocytic reaction to injury is disclosed in in vivo models. Data from in vitro studies suggest that a time-dependent involvement of different purinergic and pyrimidinergic mediators can be envisaged (Table 1). For instance, concentrations of adenine-based molecules (i.e., ATP and its breakdown products ADP and adenosine) are dramatically increased soon after injury, due to the increase in exitotoxic neurotransmission and to the cell death-associated leakage of cytoplasmic content. Thus, although long-term trophic effects have been described (see Section 2.1.1), these molecules and their specific receptors might play a predominant crucial role during the early phases of reactive astrogliosis. Conversely, uracil nucleotides could be massively released at later stages, during the deposition of CSPGs composing the glial scar (see Section 2.1.1), and could therefore contribute to long-term remodeling processes.

Given the fully supportive features of astroglia reactivity in the immature brain and the stem cell properties of germinative astroglia, the implementation of an immature gliotic response and/or of progenitor features in reactive astroglia may result in beneficial repair and endogenous cell replacement. Studies aimed at assessing this possibility are in their infancy and very little information is available at the moment on this topic. For example, a prolonged in vitro exposure to the cytokine TGFα acting via the EGF receptor (Table 1) has been shown to induce a progressive and functional reversion of astrocytes first to a radial glia-like phenotype, and later to cells that exhibit properties of neural stem cells [43]. Notably, in vivo TGFα delivery after spinal contusion positively modified the chemical and physical astrocyte-derived components of the glial scar by rendering astrocytes more mobile and conducive to axon growth (Table 1) [159]. Although no clear implementation of functional recovery was observed, this study establishes a first correlation between the acquisition of immature/stem cell properties by differentiated astrocytes and the development of more favorable gliotic traits. Along this line, recent studies have examined the effects of the manipulation of molecular pathways upregulated after injury and active in the germinative areas where they control the properties and behavior of neural stem cells. For example, administration of the morphogenic factor Sonic hedgehog (Shh) in the intact cortex [160] has been suggested to evoke stem cell properties presumably in parenchymal astrocytes and to stimulate their dormant neurogenic potential in vivo [161]. Similarly, manipulations of the BMP-nogging pathway instructing adult neurogenesis [162] and upregulated upon lesion [163,164], induces glial phenotypes suggestive of multipotency [163]. Furthermore, amongst anti-neurogenic factors possibly restricting multipotency and neurogenesis in parenchymal glia, Notch signaling is activated in response to injury [164], its blockade both promotes neurogenesis attempts from parenchymal precursors [165] and reduces brain damage after lesion [166], suggesting that its neutralization might relieve some inhibition operating on astroglia and support healing astroglia phenotypes. Nevertheless, further studies are needed to assess whether the obtained changes in astrocyte behavior can drive effective and long-term reparative responses, or, in some cases, to understand whether they are specifically responsible for the described functional improvements or plastic events.

6. Conclusions and future perspectives

Emerging evidence suggests that, in neurodegenerative diseases, manipulation of glial pro-regenerative capacities may help attenuating neuronal loss and promoting functional repair. Based on the dual role of astrogliosis (i.e., beneficial/detrimental with respect to tissue preservation/neuroprotection, tissue repair and functional recovery), ideal approaches should inhibit the deleterious effects associated with neuroinflammation while preserving the inflammatory pathways that lead to neuroprotection and sustain regenerative responses in terms of circuit reorganization and cells replacement. Unfortunately, this strategy finds its limits in the tight cross-talk amongst the molecular pathways active in astrogliosis and in their widespread mediation of both beneficial and detrimental effects, suggesting that any attempt to interfere with negative traits will also affect reparative functions. However, the actual dynamic view of gliosis reveals that distinct detrimental effects are occurring at specific time points during the response to acute lesions or are specifically harmful when persisting chronically. On the basis of this knowledge, therapeutic approaches might be designed to inhibit deleterious effects during well-defined time windows or in specific types of injury. In addition, the emerging progenitor/stem cells functions of astrocytes may open novel therapeutic avenues based on the neutralization of restrictive factors and/or the enhancement of supportive signals to potentiate the recapitulation of stem/developmental capabilities in non-germinal astrocytes reacting to damage. Although the genetic manipulation of the various biochemical pathways has allowed understanding their relative importance in the modulation and control of astrogliosis, it is now clear that selective pharmacological tools are needed to be developed as potential drug candidates to translate the current basic knowledge on astrocyte function into effective therapeutic strategies.

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