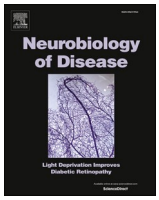
Neurobiology of Disease 185 (2023) 106231

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Do astrocytes act as immune cells after pediatric TBI?

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ARTICLE INFO

Keywords:
Astrocyte
Pediatric traumatic brain injury
Inflammation
Blood-brain barrier
Microglia
Neuro-vascular unit
Cytokines
Preclinical models

ABSTRACT

Astrocytes are in contact with the vasculature, neurons, oligodendrocytes and microglia, forming a local network with various functions critical for brain homeostasis. One of the primary responders to brain injury are astrocytes as they detect neuronal and vascular damage, change their phenotype with morphological, proteomic and transcriptomic transformations for an adaptive response. The role of astrocytic responses in brain dysfunction is not fully elucidated in adult, and even less described in the developing brain. Children are vulnerable to traumatic brain injury (TBI), which represents a leading cause of death and disability in the pediatric population. Pediatric brain trauma, even with mild severity, can lead to long-term health complications, such as cognitive impairments, emotional disorders and social dysfunction later in life. To date, the underlying pathophysiology is still not fully understood. In this review, we focus on the astrocytic response in pediatric TBI and propose a potential immune role of the astrocyte in response to trauma. We discuss the contribution of astrocytes in the local inflammatory cascades and secretion of various immunomodulatory factors involved in the recruitment of local microglial cells and peripheral immune cells through cerebral blood vessels. Taken together, we propose that early changes in the astrocytic phenotype can alter normal development of the brain, with long-term consequences on neurological outcomes, as described in preclinical models and patients.

Abbreviations: 20-HETE, 20-hydroxyeicosatetraenoic acid; ABCA1, ATP-binding cassette A1; AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; AQP, aquaporin; ATP, adenosine triphosphate; BAI1, brain-specific angiogenesis inhibitor 1; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; C1q, complement component subunit 1q; Ca^{2+}, calcium; CA1, *cornu ammonis* 1; CBF, cerebral blood flow; CCI, controlled cortical impact; CCL2, chemokine (C-C motif) ligand 2; CD, cluster of differentiation; CHILD, closed-head injury with long-term disorders; CLDN5, claudin-5; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; Cx43, connexin 43; CXCL10, chemokine (C-X-C motif) ligand 10; DAMPs, damage-associated molecular patterns; DNA, deoxyribonucleic acid; DNMT1, DNA methyltransferase 1; EAE, autoimmune encephalomyelitis; eNOS, endothelial NO synthase; FPI, fluid percussion injury; Gas6, growth arrest-specific 6; GCS, Glasgow coma scale; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GLUT1, glucose transporter 1; GPR56, G-protein coupled receptor 56; HMGB1, high-mobility group box 1; IBA1, ionized calcium-binding adaptor molecule 1; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; IgG, immunoglobulin G; IL, interleukin; JAK, janus kinase; JAMA, junction adhesion molecule-A; Kir4.1, inwardly rectifying potassium; LIF, leukemia inhibitory factor; LPR1, low-density lipoprotein receptor-related protein; LPS, lipopolysaccharide; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; microRNA, micro ribonucleic acid; MEGF10, multiple EGF-like-domains 10; MERTK, myeloid-epithelial-reproductive (MER) receptor tyrosine kinase; MMP-9, matrix metallopeptidase 9; MS, multiple sclerosis; mRNA, messenger ribonucleic acid; NAcc, *nucleus accumbens*; NF-κB, nuclear factor of kappa light polypeptide gene enhancer in B cells; Ngn, neurogenin; NLRC, NLR family caspase recruitment domain (CARD)-containing protein; NLRP2, NACHT, LRR and PYD domains-containing protein 2; NO, nitric oxide; NPC, neural precursor cells; PND, post-natal day; S1BF, primary sensory barrel field; SI/NB, substantia innominata/nucleus basalis; siRNA, small interfering ribonucleic acid; SPARC, secreted protein acidic rich in cysteine; STAT, signal transducers and activators of transcription; TBI, traumatic brain injury; TGFβ1, transforming growth factor β1; TLR, toll-like receptors; TNFα, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VEGI, vascular endothelial growth inhibitor; VSMCs, vascular smooth muscle cells; WD, weight drop; Wnt, wingless and int-1.

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https://doi.org/10.1016/j.nbd.2023.106231
Received 13 April 2023; Received in revised form 28 June 2023; Accepted 15 July 2023
Available online 17 July 2023

1. Astrocytes: from the morphology to the molecular signatures

1.1. Astrocyte morphology from GFAP immunolabelling

Astrocytes belong to the glial cell types in the central nervous system (CNS), which also include oligodendrocytes, microglial cells and ependymal cells (Freeman, 2010; Oberheim et al., 2012; Bedner et al., 2020; MacDonald et al., 2021). The term "astrocyte" was introduced by von Lenhossek in 1893 based on the cell's morphology, consisting of soma and star-like branching processes (Lenhossék, 1893). They are in close contact with neurons and their synapses, the vasculature of the brain (endothelium) (Sosunov et al., 2014) and other cell types (inflammatory cells, microglia and oligodendrocytes). Astrocytes, initially classified as "protoplasmic" in the grey matter or "fibrous" in the white matter (Oberheim et al., 2012), exhibit a higher degree of heterogeneity between brain regions with different morphologies, molecular makers and varying functions (Schober et al., 2022) and across species (Falcone, 2022). Glial fibrillary acidic protein (GFAP), a major intermediate filament composing the cytoskeleton, is the most commonly used astrocytic marker in normal and pathological CNS. GFAP-positive astrocytes in rodents are fibrous or protoplasmic. Human fibrous astrocytes are approx. 2.14-fold larger in diameter than their mouse counterparts (Oberheim et al., 2009). Rodent protoplasmic astrocytes have a less complex architecture in terms of process length and branching than Human protoplasmic astrocytes (Oberheim et al., 2006). It has been suggested that morphological complexity of astrocytes could be linked to the evolution of human cortex and its cognitive functions. Indeed, the glia-to-neuron ratio increases with the stage of evolution of mammalian species, from 0.4 in rat to 1.0 in human adult brain and interestingly 1.4 in the human cortex (Vasile et al., 2017). This difference between rodents and humans in the glia-to-neuron ratio needs to be considered in the interpretation of rodent preclinical studies.

Importantly, GFAP-immunolabelling does not label all astrocytes, therefore a combination of different astrocytic markers is more appropriate to better depict the heterogeneity of the astrocyte population. In addition to GFAP, there are other astrocytic proteins (structural proteins, metabolic markers, membrane proteins and transcription factors) which can be used as cell markers (Jurga et al., 2021). Immature astrocytes express several structural proteins that play a critical role in their differentiation and maturation, including the intermediate filament proteins such as vimentin, nestin, and synemin (Potokar et al., 2020; Jurga et al., 2021). Recently, transcriptomic and proteomic research in astrocytes has revealed molecular differences between brain regions and even within regions, for example cortex, cerebellum, striatum, hippocampus and hypothalamus (Chai et al., 2017; John Lin et al., 2017; Miller et al., 2019; Morel et al., 2019; Batiuk et al., 2020), suggesting a diversity in astrocyte responses in brain pathophysiology. This new knowledge has added a level of complexity to classification debates of astrocyte populations and circuits, which are still ongoing and require further research (Khakh and Sofroniew, 2015).

1.2. Physiological roles of astrocytes in the healthy brain

The purpose of this review is to examine the response of astrocytes following traumatic brain injury (TBI) during brain development. A brief review of the functional roles of the astrocytes in the healthy brain is important to better understand the consequences of astrocyte changes induced by TBI on the pathogenesis and/or recovery. Astrocytes are multitasking cells (Fig. 1) which: 1) regulate functions of synapses and neuronal networks during development; 2) are involved in brain homeostasis (e.g., potassium, glutamate buffering) and energy metabolism (e.g., delivery of lactate); 3) play an important role in the development and maintenance of the blood-brain barrier properties as well as the regulation of the cerebral blood flow (Jurga et al., 2021); and 4) have distinct functional roles, which vary depending on the brain region. For more details on astrocyte functions in the healthy brain, please refer to the following recent reviews (Vasile et al., 2017; Vainchtein and Molofsky, 2020).

1.2.1. Astrocyte role in the establishment and regulation of neural networks

Brain injury occurring early in post-natal period can impact brain development. Astrocytes are known to play a critical role in neuronal network maturation. To better appreciate the impact of traumatic brain injury (TBI) on immature brain circuits, it is important to briefly review current knowledge about the roles of astrocytes in brain development.

1.2.1.1. Astrogenesis. Neural precursor cells (NPC) are capable of generating both neurons and astrocytes in mammals as previously

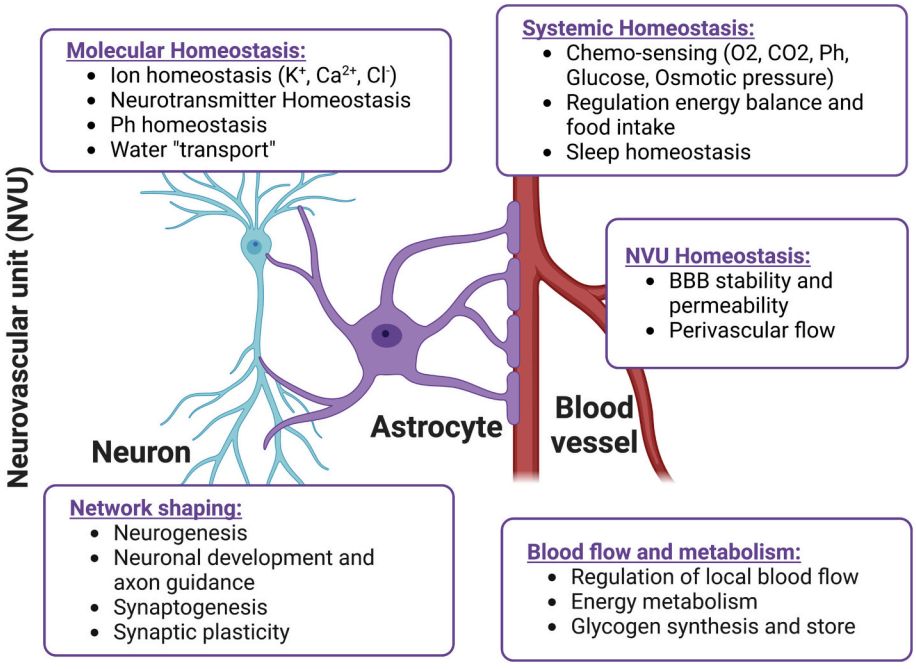

Fig. 1. Roles of astrocytes in brain development and in mature brain. Astrocytes have a unique position within the neuro-vascular unit (NVU) as astrocytic end feet cover blood vessels and astrocytic processes are in close proximity with neurons (soma, dendrites, axons and synapses). Astrocytes are involved in the NVU homeostasis, blood flow, energy metabolism, neuronal networks by regulating neuronal survival, synaptogenesis and synaptic plasticity. [Image created with BioRender]. BBB - blood-brain barrier

reviewed (Freeman, 2010). After neurogenesis onset (Takouda et al., 2017), a change in the potency of progenitor cells produces immature astrocytes in the late embryonic period (in mice >E18) (Freeman, 2010; Schober et al., 2022). Epigenetic mechanisms (DNA methylation, histone modifications and microRNA) are involved in astrocyte development (Neal and Richardson, 2018). The switch to astrogenesis in NPC is regulated by a repressive Polycomb group complex, which shuts down the expression of neurogenin 1 (*ngn1*) and *ngn2*. Then, JAK-STAT and Notch signaling pathways activate the expression of specific astrocytic genes by demethylation of their promoters via DNA methyltransferase 1 (DNMT1). In rodents, astrocytes develop their specific transcriptomic profile, morphology and cytoarchitecture during the first 3 post-natal weeks (Bushong et al., 2002; Ogata and Kosaka, 2002), when they proliferate and migrate from subventricular zone to pia mater (Schober et al., 2022). The second and third postnatal weeks (post-natal days 8–21, PND) in rodents correspond to early infancy in humans based on brain maturation timelines (Delage et al., 2021). Starting in the first week of post-natal development (PND7), astrocyte processes are undergoing rapid growth and at this time-point neighboring astrocytes have significant overlap of processes (Freeman, 2010). By PND21 astrocytes acquire their mature morphology, densely infiltrating the neuropil and occupying their exclusive spatial domains with minimal overlap (Bushong et al., 2002). There is important molecular cross-talk between astrocytes, neurons and microglia during early post-natal development (Vainchtein and Molofsky, 2020) that could play an important role in astrocyte specification (Molofsky et al., 2012). Thus, positional identity of astrocyte populations could arise from the interactions with the local environment during development.

1.2.1.2. Astrocyte role in synaptogenesis in the developing brain. Astrocytes play crucial roles in regulating brain circuit formation and function (Chung et al., 2015). Astrocytes are involved in synaptic consolidation during brain development, when active synapses are stabilized and inactive synapses eliminated (Fig. 2A, B). Both astrocyte maturation and synaptogenesis are coordinated in time: the peak of synaptogenesis occurs during post-natal weeks 2–3, rapidly after the initiation of astrogenesis (Freeman, 2010). Astrocytes influence synapse maturation by secreting inducers of synaptic formation and maturation, e. g. thrombospondins, transforming growth factor β1 (TGFβ1), hevin (secreted protein acidic rich in cysteine (SPARC) family protein), cholesterol, brain-derived neurotrophic factor (BDNF) and other molecules as previously reviewed (Clarke and Barres, 2013; Chung et al., 2015). In concert with microglia cells, astrocytes eliminate synapses in the developing and adult mouse CNS via phagocytic receptors MEGF10 (Multiple EGF-like-domains 10) and MERTK (MER receptor Tyrosine Kinase) to maintain circuit homeostasis (Chung et al., 2013; Lee et al., 2021). Regulatory functions of astrocytes in neuronal network maturation can be impaired by a TBI event during brain development as discussed below.

1.2.1.3. Astrocyte regulation of neuronal networks in adulthood. Astrocytes maintain and control different brain circuits and their associated functions (Nagai et al., 2021) by regulating the inter-neuronal communications at the synaptic level. Adult astrocytes are in close physical contact with neurons (their somas, axons, dendrites) and their synapses (Arizono et al., 2020). Astrocytes are structural and functional parts of the synapse as astrocytic processes wrap up presynaptic and postsynaptic membranes (Fig. 2A) (Allen and Eroglu, 2017). In addition, individual astrocytes occupy primarily distinct volumes of tissue in rodents (Bushong et al., 2002; Ogata and Kosaka, 2002), with non-overlapping territories in the cortex and the hippocampus (Halassa et al., 2007). These distinct astrocytic "domains", also called synaptic islands, cover between 20,000 and 140,000 synapses (Bushong et al., 2002; Ogata and Kosaka, 2002; Halassa et al., 2007). In the human brain, an astrocytic domain can be associated with 270,000 to 2 million synapses (Oberheim et al., 2009), giving the potential to locally integrate information from many synapses and providing exceptional computational power (Vasile et al., 2017) (Fig. 2A, B).

Importantly, astrocytes can monitor the activity of the synapse via neurotransmitter receptors and modulate the activity of the synapse by releasing signaling molecules such as glutamate, D-serine, lactate and ATP (Henneberger et al., 2010; Chung et al., 2015; Harada et al., 2016). Astrocyte-neuron interactions are highly dynamic as astrocytic processes can rapidly extend and retract from postsynaptic dendritic spines (Murai et al., 2003; Haber et al., 2006; Bernardinelli et al., 2014). Thus, astrocytes contribute to plasticity and homeostasis of neural circuits (Allen and Eroglu, 2017) (Fig. 2A, B).

1.2.2. Astrocyte role at the blood-brain interface

Astrocytes belong to the neuro-vascular unit (NVU), a physiological and functional unit composed of neurons, endothelial cells, vascular smooth muscle cells (VSMCs), pericytes and glial cells (astrocytes, oligodendrocytes and microglia) (Fig. 1). The NVU regulates the local cerebral blood flow, energy metabolism and contributes to the blood-brain barrier properties (Kugler et al., 2021) (Fig. 2C, D). The term "blood-brain barrier" (BBB) describes a highly selective interface between CNS and circulating blood due to presence of endothelial tight junction proteins (claudin 5, occludin), expression of transporters (glucose transporter 1, GLUT1, P-glycoprotein, etc.) and enzymes, contributing to exchange between both compartments.

Astrocyte end feet, which are in contact with blood vessels, are specialized structures (Oberheim et al., 2009) (Fig. 2C), covering up to 99% of the blood vessels in rat hippocampus as demonstrated using electron microscopic 3D reconstruction (Mathiisen et al., 2010). Astrocyte end feet express various channels including potassium channels (e. g., inwardly-rectifying potassium channel Kir4.1) (Fig. 2C), water channel-forming protein aquaporin 4 (AQP4) and connexins 43 and 30 (Cx43 and Cx30) (Nwaobi et al., 2016; Friscourt and Badaut, 2018). These channels contribute to brain water and ion homeostasis. Astrocytes with their end feet form a large network due to gap junctions, mostly formed by Cx43 and Cx30 (Chew et al., 2010).

Astrocytes, with other cells of the NVU, coordinate local cerebral blood flow to match neuronal energy demand during enhanced neuronal activity (Masamoto et al., 2015; Institoris et al., 2022) (Fig. 2C). Communication between astrocytes and endothelial cells (vascular–astrocyte coupling) leads to changes in vascular diameter (reviewed in (Filosa et al., 2016)). Nearly every astrocyte is in direct contact with at least one blood vessel and the extent of interdigitation of astrocytic processes increases around blood vessels (Bushong et al., 2002). In the human cortex GFAP-positive astrocytes processes can contact up to five different blood vessels (immunostained with AQP4) and eight neuronal cell bodies (positive for MAP2), constituting an astrocytic domain (Oberheim et al., 2006). Importantly, the vessels can be "shared" between different astrocytes. Astrocytes release vasoactive molecules (epoxyeicosatrienoic acids, prostaglandin E_2, 20-HETE or K^+) from their end feet to regulate vascular tone via action on VSMCs of parenchymal and pial arterioles (Filosa et al., 2016). This process involves neuronal activity-dependent increases in astrocytic Ca^{2+} activity, which is glutamate-mediated (Zonta et al., 2003). Astrocytic Ca^{2+} transients increase cortical arteriolar dilation in awake mice following prolonged sensory whisker stimulation (Institoris et al., 2022). The astrocyte regulation of blood flow and metabolism has been primarily demonstrated in cerebral cortex, but it is important to note these regulatory relationships can differ between brain regions.

Perivascular end feet are actively involved in energy metabolism and contain a complex network of mitochondria (Müller et al., 2018; Oberheim et al., 2009; Mathiisen et al., 2010; Bergami and Motori, 2020). End feet are equiped with glucose transporter GLUT1 for glucose uptake by astrocytes (Morgello et al., 1995). Astrocytic glucose can be converted to lactate; and then exported to synapses via monocarboxylate transporters to be used as a fuel by the neurons (Magistretti

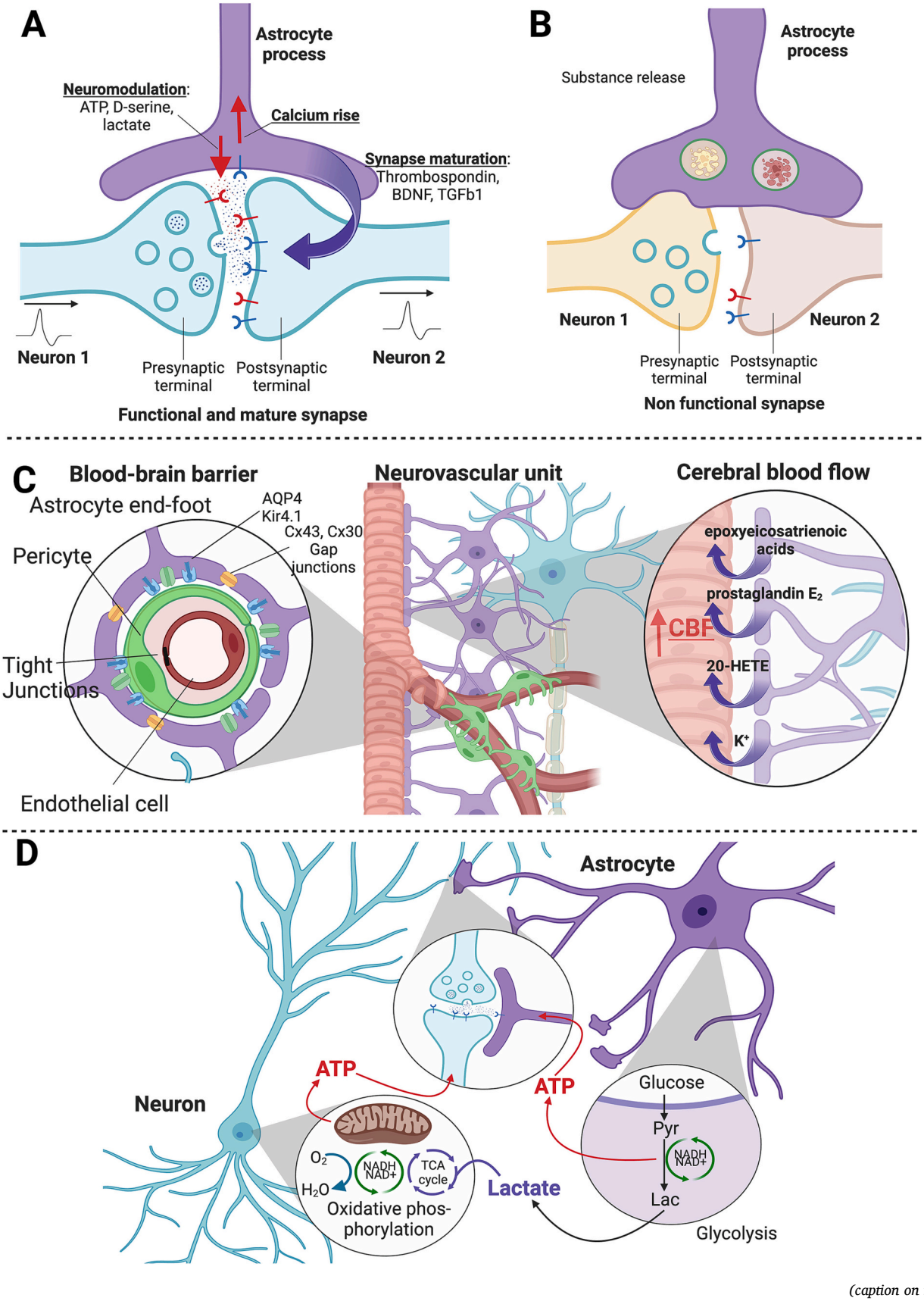

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Fig. 2. Astrocytes roles in synaptic transmission tuning (A), non-functional synapse elimination (B), the neurovascular unit (NVU) (C) and neuronal metabolism (D).

(A) Astrocytic end feet around the synaptic bouton regulate synaptic activity (by releasing gliotransmitters, such as D-serine) and maturation (by secretion of growth factors, including BDNF).

(B) Astrocytic end feet contribute to the elimination of inactive synapses through phagocytosis during brain development and in mature brain.

(C) In the neurovascular unit, astrocytes (purple) control the function of blood vessels (red), along with neurons (blue): 1) They play roles in the homeostasis of the perivascular space and in the maintenance of the blood-brain barrier through the activity of a variety of ion channels and tight junctions. 2) They increase the cerebral blood flow (CBF) after neuronal activation through the release of vasoactive compounds (e.g., prostaglandin E2), which act on vascular smooth muscle cells (pink).

(D) The astrocyte-neuron lactate shuttle is schematically presented: glucose is captured by vascular end feet, converted from pyruvate (Pyr) to lactate (Lac) and finally released into the synpase. In neurons, lactate serves as an energy substrate for ATP production. [Image created with BioRender].

20-HETE - 20-hydroxyeicosatetraenoic acid, AQP4 – aquaporin 4, ATP - adenosine triphosphate, BDNF - brain-derived neurotrophic factor, CBF - cerebral blood flow, Cx – connexin, Kir4.1 - inwardly rectifying potassium, Lac – lactate, NAD - nicotinamide adenine dinucleotide, Pyr – pyruvate, TCA - tricarboxylic acid, TGFβ1 - transforming growth factor β1.

and Allaman, 2018; Roosterman and Cottrell, 2020) (Fig. 2D). Astrocytes can also transport glucose from their end feet to the synapses via endoplasmic reticulum (Müller et al., 2018). Following glycolytic conversion to pyruvate, glucose can be utilized as an energy substrate by astrocytic mitochondria (Bergami and Motori, 2020).

1.2.3. Astrocytic network heterogeneity in different brain regions

Recent transcriptomic and proteomic data have shown heterogenous astrocytic subpopulations with important regional differences including, the somatosensory cortex, hippocampus, caudate-putamen, nucleus accumbens (NAcc), thalamus, and hypothalamus (Morel et al., 2017; Chai et al., 2017). For example, GFAP was highly expressed in the hippocampus contrary to the striatum and conversely, the gene encoding μ-crystallin (*Crym*) was highly expressed in striatal, but not in hippocampal astrocytes (Chai et al., 2017). A recent study revealed distinct transcriptomic signatures between astrocytic sub-populations within the hippocampus (Batiuk et al., 2020) and within different cortical layers (Lanjakornsiripan et al., 2018), thus further illustrating the intra-regional complexity of astrocytic networks.

Past morpho-functional studies have demonstrated differences in astrocyte behavior and function between brain regions. In the supraoptic nucleus of hypothalamus, dynamic morphological plasticity of astrocytes is essential for optimizing glutamate transmission and oxytocin neuronal activity (Panatier et al., 2006; Theodosis et al., 2006; Li et al., 2021). A reduction of astrocytic coverage of oxytocin neurons by retraction of end feet has also been well described in lactation, parturition or chronic dehydration (reviewed by Oliet and Bonfardin, 2010). Astrocyte plasticity has been also observed in other brain structures, such as in hippocampus, where astrocytic release of D-serine enables long-term potentiation in CA1 excitatory synapses (Henneberger et al., 2010). Astrocytes modulate long-term synaptic plasticity and various memory processes in the adult hippocampus (reviewed in (Wang et al., 2022)).

Regional differences between astrocytes in the hippocampal CA1 and the dorsolateral striatum were found (Chai et al., 2017) with "synaptic islands" being larger in the striatum than in the hippocampus and including more neuronal cell bodies (approx. 20 to 1 ratio). In the hippocampus astrocytic domains contact more excitatory synapses and the physical interaction of processes with those synapses is tighter than in the striatum. Similarly, astrocytes in the limbic system, specifically in the NAcc, show Ca^{2+}-signaling properties that seem to integrate inputs from other brain regions (the prefrontal cortex, the basolateral amygdala, the ventral hippocampus) (Serra et al., 2022). Striatal astrocytes respond to cortico-striatal stimulation by increasing Ca^{2+} levels (Cavaccini et al., 2020), which is critical for long-term depression and regulation of medium spiny neurons involved in striatal motor function (reviewed in (Khakh, 2019). Astrocyte Ca^{2+}-signaling contributes to various physiological functions such as odor perception in the olfactory bulb, motor skill learning in the primary motor cortex, fear conditioning and spatial learning in the hippocampal CA1 region, psychomotor behavior in the NAcc and circadian rhythms in the suprachiasmatic nucleus of the hypothalamus (Nagai et al., 2021). Astrocytic subpopulations display differences in morphology, protein expression and dynamics of calcium signaling, but also in the molecular signatures between regions in adult brain, as previously reviewed (Haim and Rowitch, 2017; Westergard and Rothstein, 2020). Astrocytic heterogeneity results in functional pathophysiological differences between brain regions. For example, hypothalamic astrocytes control systemic glucose metabolism, insulin sensitivity and thermogenesis (Herrera Moro Chao et al., 2022). Obesity promotes remodeling of hypothalamic astrocyte Ca^{2+} activity specifically in the paraventricular nucleus (Herrera Moro Chao et al., 2022). In addition to the responses and contributions of astrocytes to changes in metabolism, novel approaches will be required to assess the functional differences between different regions in brain injury.

2. Pediatric traumatic brain injury

2.1. Traumatic brain injury in children

Traumatic brain injury (TBI) is caused by a sudden external and physical insult to the brain leading to physiological impairments (Delage et al., 2021). The variety of external mechanical forces, e.g. direct impact to the skull, rapid acceleration and deceleration, blast waves, or penetration injury, makes TBI a very heterogeneous and complex disease (Nizamutdinov and Shapiro, 2017). TBI severity in clinic has been classified as mild, moderate and severe using the patient's level of consciousness measured by the Glasgow Coma Scale (GCS) (McKee and Daneshvar, 2015). Adult patients presenting with low GCS scores and/or suspected intracranial hemorrhage, often undergo computed tomography (CT), but head CT scans in young children are prescribed with caution because of potential risks of ionizing radiation on developing brain (Niele et al., 2022). Overall, TBI affects about three million children worldwide each year (Dewan et al., 2016). Epidemiological meta-analysis of TBI cases from retrospective studies in more than 165,000 children has showed that 80% of injuries were classified as "mild TBI" (according to GCS). Often mild pediatric TBI is not reported to the health services and is, thus, likely to be underestimated (Schneier et al., 2006; Thurman, 2016). The initial brain injury can evolve into chronic brain alterations with cognitive impairments, persistent attention, memory and concentration deficits, and psychosocial disorders like anxiety and depression. For example, mild to severe TBI leads to reduced corpus callosum integrity and impaired interhemispheric transfer times associated with poor neurocognitive function in children at 1–5 months after injury (Dennis et al., 2015). These cognitive impairments greatly influence patients' academic and work performance and can lead to profound social dysfunction later in life, even after mild TBI (Babikian et al., 2015; Ryan et al., 2016; Babikian et al., 2015; Sariaslan et al., 2016).

A generalized concept in the 1950s and 1960s was that "plastic is fantastic" for the developing brain (Kolb and Gibb, 2011), with an overall faster and better recovery after injury (reviewed in (Anderson et al., 2011). This concept has now been revised (Giza and Prins, 2006;

Giza et al., 2009). Indeed, several studies have shown that the outcome after pediatric TBI is even worse compared to adult TBI with the same degree of severity, with more profound edema formation, higher dysregulation of cerebral blood flow (CBF), higher mortality risk and more behavioral sequelae (for review Pop and Badaut, 2011). Brain maturation is a complex, fine-tuned process with a succession of synaptogenesis, synaptic pruning, myelination, reorganization of neuronal networks, changes in basal CBF and metabolism up to age of twenty years in humans (Toga et al., 2006; Giza et al., 2009). This process is genetically programmed, but very sensitive to environmental stimuli and experience leading to dynamic modifications of structural and functional brain networks. While neuroplasticity is considered beneficial in healthy development, recent research work indicates that children aged less than 5 years are highly vulnerable to long-term deficits after TBI (Anderson et al., 2011). In general, pediatric TBI is frequently associated with poor outcomes including impairment of processing speed, attention, memory and executive functions (Babikian and Asarnow, 2009; Anderson et al., 2013; Garcia et al., 2015). The extent of these deficits depends on the nature, the severity and the location of the injury (Catroppa et al., 2008). The timing of injury during brain development is relevant to the severity of the subsequent dysfunctions. Early TBI disrupts newly established skills and potentially interferes with the course of acquisition and consolidation of later skills (Anderson et al., 2005; Catroppa et al., 2008). Therefore, neuroplasticity may turn into vulnerability depending on injury-related factors and environmental influences during certain critical periods of brain development (Anderson et al., 2013). Ten years after mild to severe TBI, children exhibited anatomical changes in hippocampus and amygdala and had impairments in intellectual abilities, particularly in processing speed, leading to long-term consequences on school performance (Beauchamp et al., 2011; Anderson et al., 2012). Moreover, in later grades in school when the level of exigency increases for more complex and efficient cognitive processing abilities, the gap between these children and their healthy counterparts was even more evident (Babikian et al., 2015; Chevignard et al., 2016; Ryan et al., 2016). Despite significant advances, little is known of the pathophysiological mechanisms underlying the

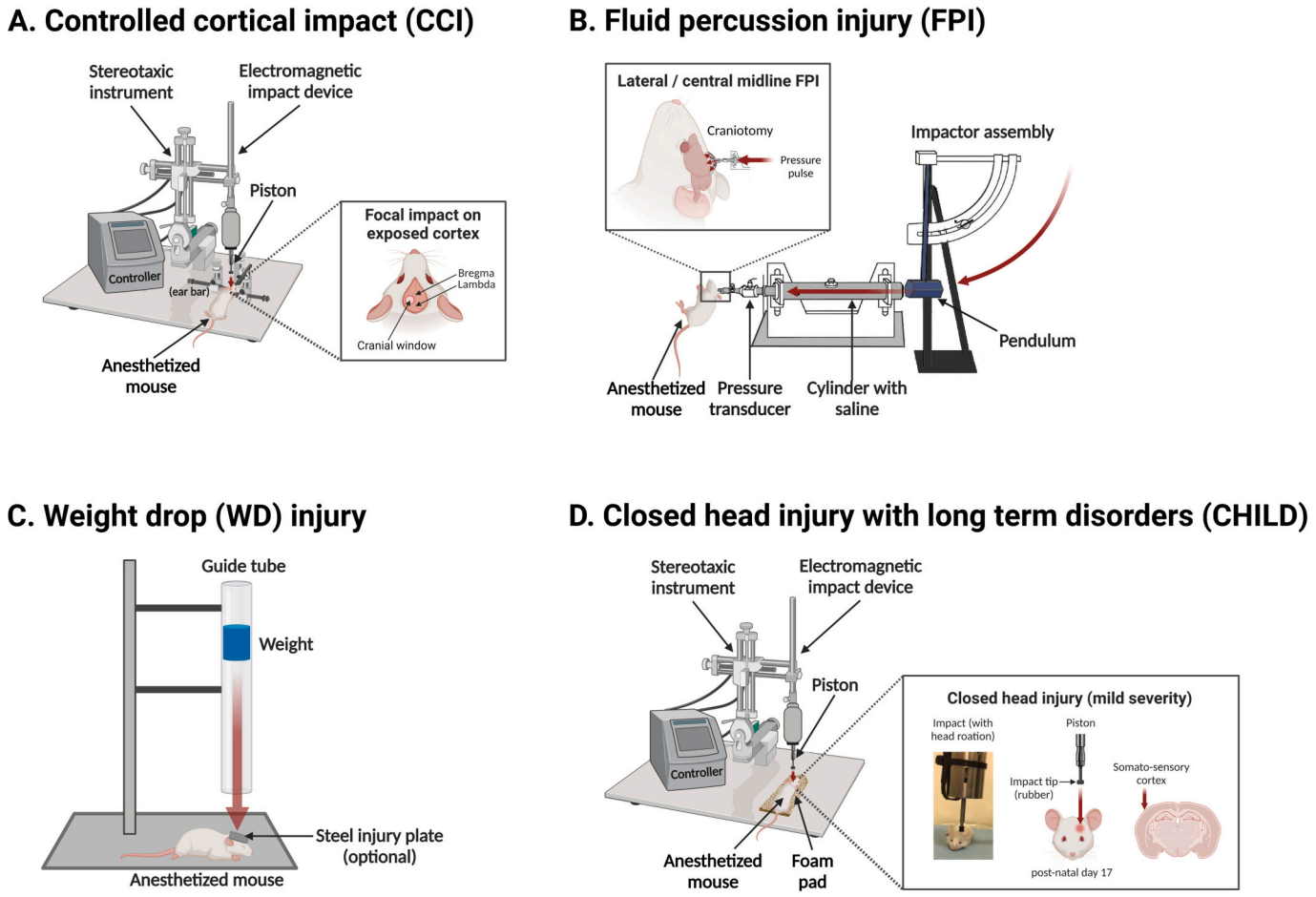

Fig. 3. Common rodent models of traumatic brain injury (TBI) induced by mechanical force. (A) The controlled cortical impact (CCI) model uses a piston driven by either a pneumatic or electromagnetic device to focally impact the exposed brain at a specified velocity and depth. The anesthetized animal's head is fixed in a stereotaxic apparatus and craniotomy is performed before the procedure. During the impact, ear bars prevent head rotation. This model is easily reproducible and mimics focal brain contusion, axonal injury, blood-brain barrier disruption and edema formation. *[adapted from* (Fournier et al., 2021)*]*. **(B)** The fluid percussion injury (FPI) model applies a brief fluid pressure pulse directly on to the intact dural surface after craniotomy. This pressure is generated by a pendulum of calibrated weight striking the cylinder filled with saline. The FPI model mimics various types of TBI depending on the position of pressure pulse (lateral or central). *[adapted from* Fournier et al., 2021 *and* Bodnar et al., *2019]*. **(C)** The weight drop (WD) model uses a tube to guide a calibrated weight dropping from a specified height on an animal head. Weight is dropped either directly on unprotected skull (mimicking focal injury) or on a steel plate which prevents skull fracture (mimicking diffuse injury). During the procedure the animal is placed on either on solid surface or on foam pad and its head is not fixed, allowing head rotation. This closed head injury model reproduces many characteristics of concussion and TBI of different severities in human. [adapted from (Bodnar et al., 2019) and (Marmarou et al., 1994)]. **(D)** The closed head injury with long term disorders (CHILD) model uses a piston with a rubber tip to impact lightly anesthetized juvenile mouse on the head with a specified velocity and impact depth. This model does not require any surgical procedure. The animal is placed on a foam pad with known elasticity and its head is allowed to rotate during impact. CHILD model mimics focal brain injury of mild severity without skull fracture. [Image created with BioRender].

consequences of pediatric TBI at short- and long-term post-injury.

Primary injury produces mechanical damage resulting in axonal stretching or shearing, hemorrhage and neuronal and glial cells death. Secondary injury occurrence is highly dependent of the severity and the location of the primary injury (Rodriguez-Grande et al., 2018; Ng and Lee, 2019; Clément et al., 2020) and can lead to increased disability and mortality (Zebrack et al., 2009). It includes a variety of inflammatory, metabolic, and vascular changes in the brain, edema formation, hypoxia and neuronal excitotoxicity linked to the excess of glutamate, known to potentially aggravate clinical outcome (McKee and Daneshvar, 2015; Sulhan et al., 2020). A brain injury, even a mild severity, occurring during the establishment of neural and astrocytic networks can have long-lasting effects on the brain and its functions (Fraunberger and Esser, 2019). In order to gain knowledge of the molecular and cellular mechanisms of the secondary injuries resulting from TBI, preclinical models are widely used.

2.2. Preclinical models of traumatic brain injury

Rodents are widely used to characterize TBI mechanisms due to their small size, easy maintenance and availability of tools for genetic modification. In pediatric rodent preclinical models of TBI, the primary injury is produced with a mechanical force directly applied to the brain typically using various apparatus that have quantifiable amplitude, duration, velocity and acceleration (Xiong et al., 2013). The rodent's head can be fixed or allowed to move freely, and with the skull opened or closed (for concussion studies). There are four common models of TBI: 1) controlled cortical impact (CCI), 2) fluid percussion injury (FPI), 3) weight drop (WD) closed head injury model and 4) closed head injury using electromagnetic or pneumatic impactor (as summarized in Fig. 3). For details on the animal models please refer to the following review papers: Marklund and Hillered (2011), Fournier et al. (2021), Delage et al. (2021). Two recent reviews from Bodnar et al. (2019) and Delage et al. (2021) nicely depict the complexity of preclinical models of TBI and show that outcomes depend on the age of injury. However, there is a lack of studies conducted on young rodents (Bodnar et al., 2019). Earlier injury (CCI at PND11, considered equivalent to human infant) induces increased tissue loss in the injured hemisphere than trauma during the juvenile period (at PND17). The anatomical changes were associated with impaired memory acquisition and cognitive deficits in rats (Raghupathi and Huh, 2007; Lengel et al., 2020). Repeated severe CCI at this age results in increased white matter atrophy compared to a single TBI (Huh et al., 2007). Neonatal brain injury at PND7 induces neuronal death and ventriculomegaly caused by the primary excitotoxicity and secondary apoptosis in rodents (Ikonomidou et al., 1996; Pohl et al., 1999; Haldipur et al., 2014; Moretti et al., 2016; Chhor et al., 2017). In response to pediatric TBI astrocytes and microglia undergo morphological and functional changes, which we will discuss it more in details further (Haldipur et al., 2014; Chhor et al., 2017).

Juvenile rodents (PND17–19) undergo active myelination and are particularly vulnerable to trauma (Sta Maria et al., 2019) during this period that corresponds to early human childhood (Delage et al., 2021; Semple et al., 2013; Rodriguez-Grande et al., 2018). Juvenile animals in moderate/severe CCI or FPI models present with neuronal tissue loss in cortex, corpus callosum, hippocampus and thalamus (Delage et al., 2021). These anatomical changes result in long-term consequences on both motor and cognitive functions (Giza et al., 2005; Ajao et al., 2012; Kamper et al., 2013; Ichkova et al., 2019). Recently, we developed a pediatric closed-head injury with long-term disorders (CHILD) model (Fig. 3D) that generates a mild concussion using an electromagnetic impactor directed to the somatosensory cortex (Rodriguez-Grande et al., 2018; Clément et al., 2020; Obenaus et al., 2023). This model incorporates both focal injury combined with head rotation in PND17 juvenile mice resulting in long-term behavioral consequences (Rodriguez-Grande et al., 2018; Obenaus et al., 2023). Juvenile mild TBI has a long-term impact not only on brain, but also on peripheral organs with chronic cardiac dysfunction observed in the CHILD model correlating with early cerebrovascular hypoxia (Leyba et al., 2023). These longterm physiological changes could be linked to systemic inflammatory response triggered by trauma (McDonald et al., 2020). Tissue remodeling is observed in this mouse pediatric TBI model with significant changes in astrocytic molecular phenotype and morphology in various brain regions (Clément et al., 2020). Injured animals present persistent anxiety-like behavior one month post impact (Rodriguez-Grande et al., 2018). One year later, the animals still have microstructural alterations and neuronal loss in the hippocampus and substantia innominata/nucleus basalis (basal forebrain) with associated glial changes (both in astrocytes and microglia) and spatial memory impairments (Obenaus et al., 2023).

Frequently, preclinical rodent models are criticized with regards to the small size of the brain and the low proportion of the white matter relative to humans (10% in mice, 14% in rat and 60% in human) potentially limiting clinical translation (Krafft et al., 2012). Rodents have a lissencephalic brain, while the human brain is gyrencephalic (Semple et al., 2013) and brain maturation differs importantly between these two species, thus making it difficult to find the correct corresponding ages (Semple et al., 2013). Moreover, human GFAP positive astrocytes exhibit a more complex morphology than rodent GFAP astrocytes (see above). To date, functional differences between human and rodent astrocytic responses to brain injury are not well understood (Castejón, 2013). Recent efforts to develop the technical capacity to detect astrocytic response to blast injury using MRI in human could help to compare TBI pathology with data obtained in rodents in the future (Benjamini et al., 2023). Several preclinical translational models of TBI exist in large animals with gyrencephalic brains, such as pigs. Indeed, brain size and anatomy, proportion between grey and white matter and the time course of myelination during development are similar between pig and human as reviewed by Kinder et al. (2019). The juvenile pig model of moderate/severe CCI demonstrated a strong astrocytic response, but the consequences of mild brain TBI remain to be elucidated (Baker et al., 2019). Several studies suggest potential sex differences in response to trauma in piglets (Missios et al., 2009), as well as differential age effects of trauma (Duhaime et al., 2000; Costine et al., 2012, 2015).

2.3. Neuroinflammation in pediatric traumatic brain injury

Neuroinflammation is a complex cascade defined by a pathological immune process in the brain to the response to a pathogen or non-pathogen insult with involvement of both the innate and adaptative immunity (Estes and McAllister, 2014; Dinet et al., 2019). It has originally been proposed that the neuroinflammation response has four hallmarks: production of proinflammatory cytokines and chemokines, glial activation (including astrocytes), changes in BBB properties and immune cell infiltration into the brain (Estes and McAllister, 2014). In TBI, neuroinflammation contributes to secondary injuries that develop minutes to months after primary brain injury and could persist at long-term (Goryunova et al., 2007; Simon et al., 2017). Despite the limited knowledge on inflammation in the context of pediatric TBI, various biomarkers related to inflammatory processes have been assessed in cerebrospinal fluid (CSF) or plasma in children with different severity of TBI (Nwafor et al., 2022). Interleukin-6 (IL-6) levels were upregulated 48 h after severe injury and were associated with better neurologic outcomes in children (Chiaretti et al., 2008). Levels of IL-1β in the CSF 2 h post-TBI correlated with the injury severity and low levels were predictive of better outcomes (Chiaretti et al., 2008). Elevated levels of IL-8 were found in CSF of children with severe TBI and correlated with poor outcomes (Whalen et al., 2000). In children with TBI, increased plasma GFAP levels predicted the presence of intracranial brain lesions which then were confirmed by CT (Papa et al., 2016). Few studies have explored the relationship between acute and long-term impacts of pediatric TBI (especially mild severity) and neuroinflammatory processes

(Nwafor et al., 2022). The contribution of inflammatory mechanisms and astrocyte responses to survival and cognitive outcomes in children remains largely unknown.

Preclinical work has proposed some putative mechanisms and a time-line of pediatric TBI-induced neuroinflammation. It consists of a combination of systemic immune activation (Jassam et al., 2017) with increseased levels of cytokines, chemokines, growth factors and local recruitment of astrocytes, microglia and immune cells to the lesion site (Lozano et al., 2015; Alam et al., 2020; Simon et al., 2017; Li et al., 2020; Faden et al., 2021; Pischiutta et al., 2022; Clausen et al., 2019; Alam et al., 2020). The exact role of neuroinflammation, beneficial or deleterious, is still debated, despite some consensus regarding the pathogenic role of chronic neuroinflammation (Lozano et al., 2015; Jassam et al., 2017). There is clearly a lack of data regarding neuroinflammatory mechanisms in neonatal, juvenile, and adolescent preclinical models of TBI (Delage et al., 2021), and the long-term impacts of juvenile TBI remains understudied (Obenaus et al., 2023).

3. Do astrocytes play an immune role in pediatric traumatic brain injury (TBI)

3.1. Astrocyte phenotype after adult TBI and pediatric TBI

The astrocyte is a primary responder to TBI and plays a key role in the initial immune response in concert with microglial cells (Fraunberger and Esser, 2019; Liu et al., 2020). Adaptive responses of astrocytes ("reactive astrocytes" or "astrogliosis") allow to quickly adapt their function and preserve CNS tissue (Khakh and Sofroniew, 2015). Severe tissue damage induces robust innate and adaptive immune responses with reactive astrocytes adjacent to the lesion forming an "astroglial scar" (Burda et al., 2016). The metaphor "scar" can be misleading as "reactive astrocytes" are not "scar tissue". "Astroglial scar" can be seen as a physical barrier crucial for isolating the lesion site and restraining the spread of inflammation and neurotoxicity to adjacent healthy regions (Sofroniew, 2020). Various signals originating from different cell types (neurons, microglia, immune cells) contribute to the transformation of astrocytes to their "reactive state" (Sofroniew, 2020). Extracellular mechanical stimuli induced by TBI increase astrocytic intracellular Ca^{2+} signals (Fig. 4), which, in turn, contributes to the increased expression of GFAP and vimentin (reviewed in (Shigetomi et al., 2019)).

Astrocytes exhibit significant GFAP-positive phenotypic changes post-injury in various preclinical pediatric TBI models (Adelson et al., 2001; Clément et al., 2020; Fletcher et al., 2021; Huh et al., 2007; Huh et al., 2008; Ichkova et al., 2019, 2020; Pop et al., 2013; Prins et al., 2010; Robinson et al., 2016; Rodriguez-Grande et al., 2018; Russell et al., 2014; Schober et al., 2019. Table 1 lists studies focusing on astrocytic responses to TBI in pediatric preclinical models (Fig. 3). In mild closed-head juvenile injury mouse model, reactive GFAP-positive astrocytes were observed in the primary site of injury, the somatosensory cortex, as well as in distant regions like the amygdala, hippocampus and corpus callosum as early as one day after impact (Rodriguez-Grande et al., 2018; Clément et al., 2020). Morphological astrocytic changes have been proposed to be a landmark of reactive astrocytes (Pekny and Nilsson, 2005; Escartin et al., 2021). Astrocytic aquaporin 9 (AQP9), a water channel, seems to play an important role in the change of astrocyte morphology following brain injury (Liu et al., 2012; Hirt et al., 2018). The extent and "propagation" of astrocytic changes depend on the initial severity of the injury (Huh et al., 2007). However, an increase in astrocytic GFAP expression was not detected short- and long-term following a mild to moderate diffuse midline FPI in PND17 juvenile rats (Green et al., 2022). Thus, glial activation depends on the type of juvenile brain injury. Therefore, using astrocytic activation markers other than GFAP alone should help to define astrocyte reactivity. Increased mRNA expression of cytokines (IL-1β, IL-6, TNF-α, TGF-1β) has been described up to 7 days after juvenile brain trauma (PND20–21) (Hamood et al., 2022). Associated with astrocyte changes, microglia cells and macrophages are recruited in the neonatal brain (Kempuraj et al., 2017; Tong et al., 2002) with increased microglial cells observed one month after injury in a model of juvenile (PND 28) CCI (Smith et al., 2019). Morphological changes of microglia cells have been described in the hippocampus even 12 months after a single mild closed head injury deliverd at PND17 (Obenaus et al., 2023). Juvenile TBI-induced changes after several months include morphologically transformed microglia (loss of ramifications, hypertrophic and/or amoeboid) expressing the phagocytic marker CD68 in the primary sensory barrel field (Doust et al., 2021; Green et al., 2022). These results, obtained in pediatric TBI models, are interesting as reactive microglia and reactive astrocytes are frequently localized together and functionally interconnected in adult TBI preclinical models (Ren et al., 2013; Witcher et al., 2018) and in human TBI patients (Morganti-Kossmann et al., 2019).

In addition to the morphological alterations of astrocytes, there are substantial transcriptomic changes. Little is known on the astrocyte in pediatric TBI, however there is growing literature on pathological molecular changes in astrocytes in adult brain. One of the first descriptions of astrocytic transcriptome profiles was performed using two different adult mouse brain disorder models: ischemic stroke and systemic bacterial lipopolysaccharide (LPS) inflammation model (Zamanian et al., 2012). Reactive astrocytes were subdivided into two distinct sub-types "A1" (neurotoxic) and "A2" (neuroprotective) based on their respective transcriptional profiles (Zamanian et al., 2012; Liddelow et al., 2017). However, this binary view of two subtypes of reactive astrocytes raises questions as to how these fit with the complexity of the pathophysiology (Escartin et al., 2021). More recently, nine subtypes of reactive astrocytes with distinct transcriptomic signatures have been described in the cortex after LPS-injection in adult mice (Hasel et al., 2021). Interestingly, reactive astrocytes showed region-specific (prefrontal *versus* visual cortex) inflammatory transcriptomic response following LPS injection (Diaz-Castro et al., 2021). So far, little is known about astrocytic transcriptomic changes in the context of TBI, even for adults. Recent studies have provided transcriptomic responses to severe brain injury using stab wound model. Microarray analysis of adult somatosensory cortex revealed 916 differentially expressed transcripts in astrocytes between injured and sham mice with up-regulation of inflammatory mediators: nuclear factor of kappa light polypeptide gene enhancer in B cells (NF-κB), tumor necrosis factor α (TNFα), IL-1β, and IL-6 (Sirko et al., 2015). The transcriptomes of microglia and astrocytes have been compared after fluid percussion injury in adult mice (Todd et al., 2021). In both glia cell types, most enriched pathways were related to innate immune response, viral defense response, response to interferon β and antigen processing and presentation of endogenous peptide antigen via MHC class I. The expression of 55 genes were impacted in astrocytes, including 15 genes overlapping with microglia, mostly interferons. To our knowledge, there is no information on the astrocyte transcriptomic response to the trauma during brain development with temporal and spatial differences between immature astrocytes subpopulations and this should be an important question to answer in the future. Mechanisms of reactive astrogliosis during brain maturation must be explored to better understand long-term impairments observed in pediatric TBI, as we have previously described in our preclinical CHILD model (Rodriguez-Grande et al., 2018; Clément et al., 2020; Obenaus et al., 2023).

3.2. Blood-brain barrier, glia limitans and its immune protective function in relation with astrocyte response

The blood-brain barrier at the endothelial level is a highly selective filtering membrane mediating bilateral exchange between the blood and the brain. Abnormal permeability of the BBB (Fig. 4) can lead to the extravasation (leakage) and accumulation of plasma-derived proteins (fibrinogen, albumin) and immunoglobulin G (IgG) (Pop and Badaut, 2011; Pop et al., 2013; Badaut et al., 2015; Rodriguez-Grande et al.,

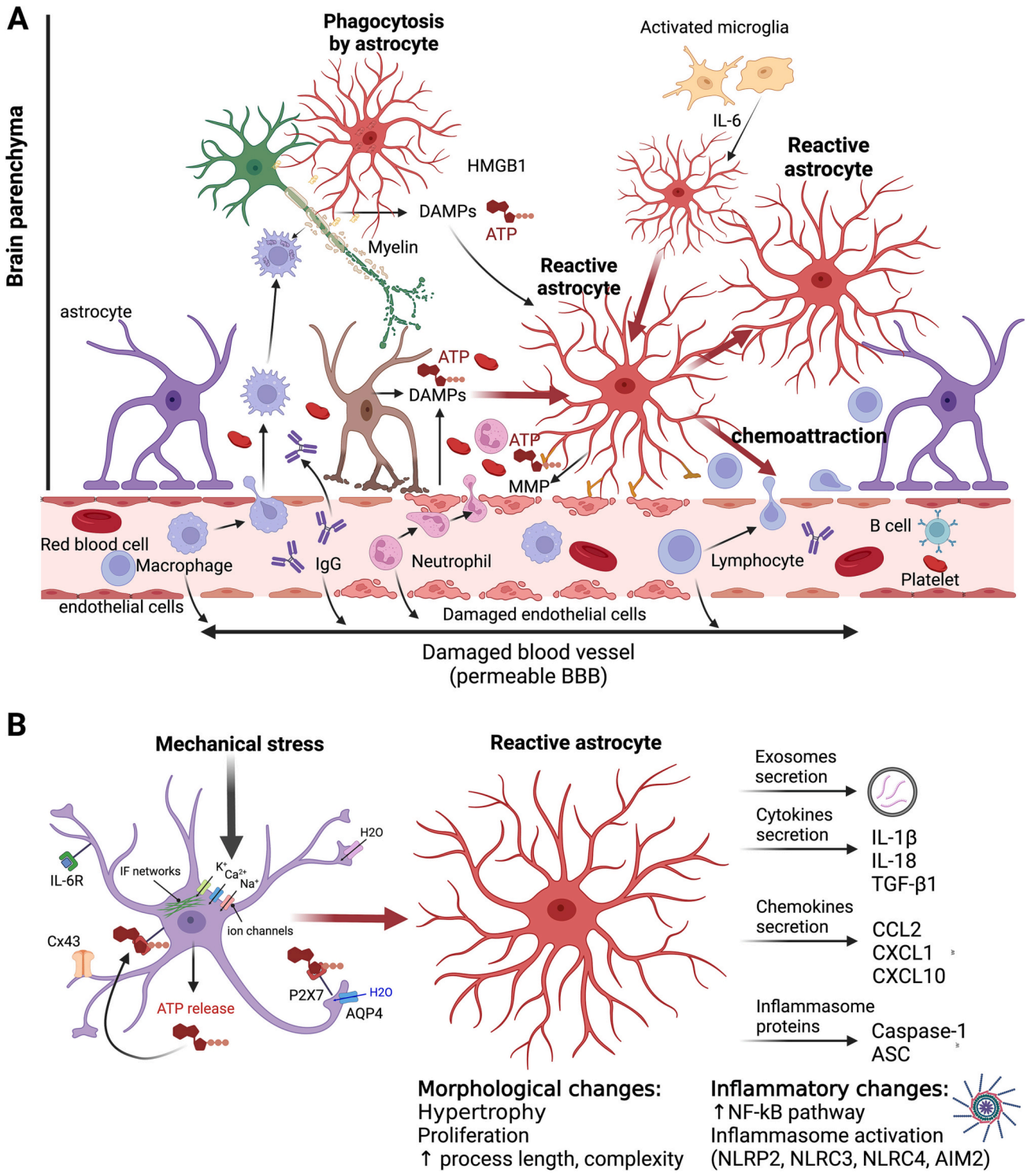

Fig. 4. Role of the astrocyte in the inflammatory cascades induced by an injury in the adult brain.

(A) Traumatic brain injury induces astrocytic changes via multiple signaling pathways. Macrophages, neutrophils and lymphocytes infiltrate the surrounding neuropil from damaged blood vessels, contributing to the elimination of cellular debris and myelin from injured neurons. Released cytokines from infiltrated cells and microglia, as well as damage-associated molecular patterns (DAMPs), contribute to the activation of astrocytes. Reactive astrocytes contribute to phagocytisis, activation of microglia, fragilization of the BBB (with MMP release) and chemoattraction of circulating immune cells to the lesion site.

(B) Mechanisms and consequences of astrocyte reactivity. Mechanical shear forces induced by injury are detected by astrocytic mechanosensitive receptors, increasing ion influx which leads to ATP release. This is followed by a rapid change of phenotype (morphological and inflammatory). [Image created with BioRender].

AQP4 – aquaporin 4, AIM2 - absent in melanoma 2, ASC - apoptosis-associated speck-like protein containing a caspase recruitment domain, ATP - adenosine triphosphate, BBB - blood-brain barrier, CCL2 - chemokine (C-C motif) ligand 2, CXCL - chemokine (C-X-C motif) ligand, Cx43 – connexin 43, DAMPs - damage-associated molecular patterns, IF - intermediate filaments, IgG - immunoglobulin G, IL – interleukin, HMGB1 - high-mobility group box 1, MMP - matrix metallopeptidase, NF-κB - nuclear factor of kappa light polypeptide gene enhancer in B cells, NLRC - NLR family caspase recruitment domain (CARD)-containing protein, NLRP2 - NACHT, LRR and PYD domains-containing protein 2, P2X7 - purinoceptor 7, TGFβ1 - transforming growth factor β1.

Table 1
Summary of the literature depicting GFAP-positive astrocytic changes in preclinical juvenile TBI (ordered in function of the age of the impact).

Days	TBI preclinical model	Time post-injury	Brain regions studied	Astrocyte changes	Species	Other astrocytic markers	References
PND 7	Weight Drop	1,5 and 21 days	N.D.	Increase of GFAP	Mouse	-	Haldipur et al., 2014
PND11	Repeated CCI	1 and 3 days	Hippocampus, cortex, corpus callosum	Increase of GFAP	Rat	-	Huh et al., 2007
PND 11	CCI	3 and 28 days	Hippocampus, cortex, corpus callosum	Increase of GFAP	Rat	-	Raghupathi and Huh, 2007
PND12	CCI	3 and 16 days	Cortex	Increase of GFAP	Rat	-	Robinson et al., 2016
PND17	CCI	3 and 28 days	Hippocampus, cortex, corpus callosum	No difference for GFAP	Rat	-	Raghupathi and Huh, 2007
PND17	CCI	1 and 4 days	Motor cortex	Increase of GFAP (mRNA)	Rat	-	Russell et al., 2014
PND17	CCI	3 and 60 days	Motor cortex, hippocampus	Decrease of GFAP after AQP4-siRNA treatment	Rat	AQP4 measurement	Fukuda et al., 2013
PND17	CCI	1,3, and 7 days	Motor cortex	Increase of GFAP	Rat	Caveolin 1and 3 changes	Badaut et al. 2015
PND17	CCI	1,3, 7 and 60 days	Hippocampus, Motor cortex	Increase of GFAP, decrease after Cx43-siRNA	Rat	Increase of connexin 43	Ichkova et al., 2019
PND17	CCI	6 months	Motor cortex, hippocampus, corpus callosum	No difference for GFAP	Rat	-	Kamper et al., 2013
PND17	CCI	3,7 and 30 days	Motor cortex, hippocampus	Increase GFAP in cortex and no change in hippocampus, with decrease at 7 days	Rat	-	Schober et al., 2019
PND17	FPI midline	2h, 1,7, 25 and 43 days	Somatosensory cortex (S1BF)	No difference for GFAP	Rat		Green et al, 2022
PND17	FPI midline	10 months	Hippocampus, cortex, white matter, zona incerta and S1BF	No difference for GFAP	Rat	-	Doust et al., 2021
PND17	WD	1,3 and 7 days	Hippocampus, corpus callosum	Increase of GFAP	Rat	-	Adelson et al., 2001
PND17	Closed head CCI device	1,3 and 8 days	Cortex	Increase GFAP 3 and 8 days	Rat	-	Huh et al., 2008
PND17	CHILD	1,7 and 28 days	Corpus callosum	Increase of GFAP	Mouse	-	Rodriguez-Grande et al., 2018
PND17	CHILD	1,7 and 28 days	Prefrontal and somatosensory cortexes, hippocampus, amygdala	Increase of GFAP in somatosensory cortex and morphological changes of GFAP-positive astrocytes in all structures	Mouse	Nestin and vimentin	Clément et al., 2020
PND17	CHILD	12 months	Substantia innominata/nucleus basalis (SI/NB), hippocampus	Decrease of GFAP the SI/NB, no change in hippocampus	Mouse	Changes of AQP4 with increase in hippocampus and decrease in SI/NB	Obenaus et al., 2023
PND21	CCI	5 weeks	Corpus callosum, external capsule	Increase of GFAP	Mouse	-	Fletcher et al., 2021
PND21	WD	1,3 and 7days	Corpus callosum	Increase of GFAP at 3 days for males and 7 days for females	Mouse	Colocalization of GFAP with μ-opioid receptors	Hamood et al., 2022
PND28	CCI	7 days	Cortex, white matter	Increase of GFAP	Pig	-	Baker et al., 2019
PND35	FPI midline	2h, 1,7, 25 and 43 days	Somatosensory cortex	No difference	Rat	-	Green et al, 2022
PND35	FPI midline	10 months	Hippocampus, cortex, white matter, zona incerta and S1BF	No difference for GFAP	Rat	-	Doust et al., 2021

Changes in GFAP expression are color-coded: increase in green, no difference in blue and decrease in orange. We used the following key words: 'astrocyte', 'traumatic brain injury', 'juvenile', 'mouse', 'rat', 'pig'. AQP4 – aquaporin 4, CCI - controlled cortical impact, CHILD - closed-head injury with long-term disorders, Cx43 - connexin 43, FPI - fluid percussion injury, GFAP - glial fibrillary acidic protein, PND - post-natal day, S1BF - primary sensory barrel field, SI/NB - substantia innominata/nucleus basalis, siRNA - small interfering ribonucleic acid, WD - weight drop.

2018), infiltration of immune cells (T and B lymphocytes, macrophages, and neutrophils) (Jassam et al., 2017) and development of edema (Badaut et al., 2019; Fukuda et al., 2013) and excitotoxicity (Baracaldo-Santamaría et al., 2022). Increased IgG, albumin and fibrinogen in brain parenchyma are considered as markers of BBB dysfunction and we have observed that IgG extravasation peaks at 1–3 days after CCI in juvenile rats (Badaut et al., 2015) and normalizes 2 months post-impact (Pop and Badaut, 2011; Pop et al., 2013). Related to BBB dysfunction, astrocytic AQP4 increases after CCI in juvenile rats and plays a role in brain edema formation following trauma (Fukuda et al., 2012). Silencing of astrocytic AQP4 using smallinterfering RNA decreases edema formation, reactive astrocytes and improves long-term cognitive outcomes after TBI (Fukuda et al., 2013).

Closed-head mild juvenile TBI also leads to cortical and white matter transient increases in IgG extravasation associated with increased water content at 1 day post impact (Rodriguez-Grande et al., 2018). These early changes in BBB permeability were associated with astrocyte reactivity and an increased level of AQP4 in white matter astrocytes'

processes and end feet, alongside with changes in vascular reactivity and vessel diameter (Rodriguez-Grande et al., 2018; Ichkova et al., 2020). Microstructural DTI changes in hippocampus and basal forebrain up to one year after juvenile mild trauma were associated with region-specific astrocytic AQP4 expression (Obenaus et al., 2023). Moreover, persistent vascular changes were observed in injured mice, as the proportion of small microvessels was decreased in the basal nuclei compared to hippocampus (Obenaus et al., 2023).

At the cellular level, tight and gap junctions are important regulators of the integrity of the BBB. Tight junctions form close physical links between endothelial cells, preventing penetration of molecules into the brain parenchyma. BBB loss of integrity is related to loss and misplacement of tight junction proteins. Astrocytes along with pericytes are key regulators of the integrity of the endothelial layer. Reactive astrocytes can modulate BBB properties during brain injury (Dinet et al., 2019). Astrocytes secrete various vascular permeability factors such as vascular endothelial growth factor (VEGF), MMP-9, nitric oxide (NO), and glutamate which induce endothelial cell apoptosis and decrease the expression of endothelial tight junctions, thus contributing to increased BBB permeability (reviewed in (Michinaga and Koyama, 2019)). In a clinical study, circulating VEGF levels were decreased on the first day after TBI but started to increase from 4 day and peaked 2 weeks after injury in adult patients, normalizing by 3 weeks (Li et al., 2016). An elevated ratio VEGF/ VEGI (vascular endothelial growth inhibitor) at 7 days after TBI has been proposed as a prognostic parameter for clinical outcomes in adult patients. Patients who had improved neurological conditions after TBI had lower levels of circulating VEGF on day 7 but higher levels on day 21 compared to patients who presented with deterioration. There is scant data available in pediatric TBI, but a rapid elevation of VEGF levels in CSF from children with severe TBI suggests rapid vascular response (22 h post-TBI) (Shore et al., 2004).

Claudin-5 (CLDN5) is the most enriched tight junction endothelial cell protein of the BBB (Greene et al., 2019). Severe TBI in adult rats induced the loss of CLDN5, occludin and extravasation of serum proteins into brain parenchyma (Başkaya et al., 1997), but BBB properties may be age-dependent. Similarly, a transient loss of CLDN5 has been observed at 3 days post-CCI performed at PND17 juvenile rats (Badaut et al., 2015), suggesting a disruption of the BBB. An increase in CLDN5 was observed in large cortical blood vessels two months after juvenile brain injury, consistent with a mechanism for functional BBB restoration (Pop et al., 2013). CLDN5 changes and increases of IgG extravasation in the juvenile CCI model can also be explained by changes in caveolin expression (Badaut et al., 2015). Caveolin proteins are involved in the formation of caveolae necessary for endo-, trans- and exocytosis in endothelial cells and their expression is altered after juvenile CCI (Badaut et al., 2015) and appear to be linked to resolution of BBB disruption. Importantly, Cav-1 and Cav-3 are expressed by reactive astrocytes following juvenile TBI, but their functional role in the reactive astrocytes remains to be elucidated.

Other astrocyte-derived factors contributing to permeability of BBB after adult TBI include matrix metalloproteases (MMP) which degrade the extracellular matrix and tight junctions at the level of endothelial cells (Abdul-Muneer et al., 2016; Zhang et al., 2016). Chemokines and inflammatory cytokines released by astrocytes and other cells up-regulate expression of endothelial cell adhesion molecules (intercellular adhesion molecule-1, ICAM-1 and vascular cell adhesion molecule-1, VCAM-1) (Michinaga and Koyama, 2019). In adult mice, ICAM-1 promotes adhesion and transmigration of leukocytes across the BBB to the injury site induced by fluid percussion via activation of matrix metalloproteinase (MMP), oxidative stress and VEGF pathways (Bhowmick et al., 2021). High levels of soluble ICAM-1 were found in children with severe TBI (Briassoulis et al., 2007). Whether ICAM-1 and lymphocyte migration could be regulated by astrocytes following pediatric trauma remains to be elucidated. Similarly, gap junction proteins such as connexin 43 (Cx43) have been implicated in immunoregulatory properties of astrocytes, by controlling recruitment and penetration of immune cells through the BBB in the adult brain (Boulay et al., 2015, 2018). Deletion of Cx43 in mice induces continuous recruitment of B- and T lymphocytes (positive for CD4 and CD8 antigens), macrophages and neutrophils (Boulay et al., 2018). However, several studies have shown increased astrocytic connexin 43 expression in adult injured brain (reviewed in (Chew et al., 2010)). An increase of Cx43 expression was observed in the perilesional cortex up to 2 months after juvenile CCI in rats and silencing of Cx43 expression using siRNA decreased GFAP-positive astrocytes and improved behavioral outcomes, such as motor function (Ichkova et al., 2019). Silencing Cx43 post-injury possibly limits water and signaling molecule Ca^{2+} diffusion by blocking gap junctions between astrocytes and limiting the spread of changes in GFAP expression (Ichkova et al., 2019). Silencing Cx43 did not mitigate edema formation or BBB dysfunctions, even though a close relation between Cx43 and AQP4 expression has been described in pediatric brain (Jullienne et al., 2018). Astrocytes can secrete vascular protective factors, such as angiopoietin-1, sonic hedgehog, glial-derived neurotrophic factor (GDNF), retinoic acid, insulin-like growth factor-1 (IGF-1) and apolipoprotein E (Michinaga and Koyama, 2019). These factors could protect endothelial cells from apoptosis and promote recovery of tight junctions. Astrocytes play a key role in the properties of the brain endothelial cells after injury, but limited studies on the role of astrocytes in pediatric TBI preclude to conclude whether astrocytic phenotypic changes are detrimental or beneficial to the blood-brain interface.

Recent studies have highlighted the potential role of astrocytes in protection of the CNS against the infiltration of lymphocytes from the peripheral blood by forming a "barrier" with expression of tight junction proteins (Horng et al., 2017). In addition to the BBB, the glia limitans could constitute a second layer of brain protection. The glia limitans is between the pia mater and the brain tissue with a layer of astrocytic end feet that are connected by tight junctions forming a protective layer as reported in an adult mouse model of autoimmune encephalomyelitis (EAE) (Horng et al., 2017; Quintana, 2017). Horng and colleagues showed that tight junction proteins in astrocyte end feet regulate the entry of immune cells and serum proteins during inflammatory response in an EAE. Treatment with pro-inflammatory cytokine Il-1β has been shown to induce the expression of CLDN1, CLDN4 and junction adhesion molecule-A (JAMA) proteins in human astrocytes *in vitro* (Horng et al., 2017). Conditional inactivation of *Cldn4* in astrocytes increases neuronal cell death and subsequently lesion area, demyelination and mortality, associated with exacerbated CD4+ and CD11b+ cells infiltration (Horng et al., 2017). These results suggest that astrocytic glia limitans can be in "close" configuration with tight junction proteins during inflammation to protect the CNS from entry of immune cells; and under physiological conditions, astrocytic glia limitans would be in "open" configuration with absence of tight junctions (Horng et al., 2017; Mora et al., 2020). To date, the role of the glia limitans in juvenile TBI hasn't been explored and could represent a new therapeutic target.

3.3. Role of the astrocytes in phagocytosis: potential phagocytic function

Appropriate clearance of dead cells by phagocytosis is necessary for development, maintenance, and regeneration of the CNS. Accumulated cell debris from axons and myelin can trigger neuroinflammation (Konishi et al., 2022). Microglial cells are an important component of innate immune system and can be considered as potential "resident macrophages" of the brain and specialized phagocytes during brain development including pathological situations. Several lines of evidence support the idea that astrocytes share phagocytic receptors with microglia, such as AXL receptor tyrosine kinase, myeloid-epithelial-reproductive tyrosine kinase (MERTK), G-protein coupled receptor 56 (GPR56), brain-specific angiogenesis inhibitor 1 (BAI1), αvβ3/5 integrin and low-density lipoprotein receptor-related protein (LPR1) as previously reviewed (Konishi et al., 2022). The receptor multiple EGF-like-domains 10 (MEGF10) is specific to astrocytes and plays a role in circuit refinement during brain development and in adulthood (Chung

et al., 2013). Mouse primary cortical astrocytes phagocyte neighboring laser-damaged astrocyte cells *in vitro* (Wakida et al., 2020). In pathological situations, myelin debris is detected in astrocytes at sites of acute myelin breakdown in autopsy brain tissue of adult patients with various demyelinating CNS diseases (Ponath et al., 2017). Astrocytic phagocytosis of myelin debris via LPR1 receptor results in activation of pro-inflammatory NF-κB pathway *in vitro* (Ponath et al., 2017), which regulates cytokine production and cell survival in inflammatory states (Liu et al., 2017). NF-κB activation leads to secretion of lymphocyte- and macrophage-attracting chemokines by astrocytes and culture medium from myelin-treated rat astrocytes increased directed migration rates of CD4+ T helpers and microglia (Ponath et al., 2017). Astrocytes show phagocytic properties following ischemia with astrocytic processes enwrapping neuronal debris and expressing galectin-3, a phagocytic biomarker (Morizawa et al., 2017). Astrocytic ATP-binding cassette A1 (ABCA1) is crucial in triggering the phagocytic function in astrocytes. Myelin uptake could be an early response of astrocytes in disease such as stroke and adult TBI. The phagocytic capacity of reactive astrocytes is mediated by AXL / signal transducer and activator of transcription 1 (STAT1) / ABCA1 pathway in adult mouse CCI model (Zhou et al., 2021). Intraventricular injection of the specific AXL ligand growth arrest-specific 6 (Gas6) promoted phagocytic function in cortical astrocytes of injured mice. Pharmacological activation of AXL by Gas6 attenuated TBI effects on the expression of IL-6, TNFα, and IL-1β and improved motor coordination deficits and neurological severity scores at 3 and 7 days after injury (Zhou et al., 2021). Reactive astrocytes also phagocyte degenerated synapses, cells and myelin in human adult severe TBI patients as shown by electron microscopy (Castejón, 2013). Thus, astrocytic phagocytosis plays an important role in TBI pathology, protecting healthy brain tissue from damaged neurons and cell debris and limiting neuroinflammation. It is important to further explore the phagocytic ability of astrocytes in different brain regions in relation to pediatric TBI.

3.4. Immune role of astrocytes following adult traumatic brain injury

The immune system is hard to perceive of anatomically in contrast to the nervous system (CNS), but the immune system is much better described functionally than the CNS. This also means that beyond bone marrow-derived leukocytes, other cells, for example epithelial cells can be considered to have immune functions (Paludan et al., 2021). And while the distinction of non-self from self has long been considered the main function of the immune system, a more recent view proposes that it detects antigenic discontinuity (Pradeu et al., 2013). Similarly to the immune system in periphery, astrocytes are behaving as sensors of micro-environmental changes in neuropil in healthy or injured brain like the microglial cells. Mechanical stress, homeostasis changes and paracrine immune signals are detected by astrocytes, triggering various changes in astrocyte properties. Astrocyte responses are rapid in order to prevent brain injury expansion by different processes depending on the type, gravity and location of the injury (Burda et al., 2016). Astrocytes assure neuroprotection and can form a protective quasi-permanent "astroglial scar" surrounding the lesion site in the case of severe injuries (Sofroniew, 2020). Different sub-populations of cortical astrocytes project their processes after brain injury to the lesion site (Bardehle et al., 2013). The diversity in the astrocyte responses is a key part of CNS innate immunity (Sofroniew, 2020). Vascular and parenchymal cells damaged during primary brain injury release damage-associated molecular patterns (DAMPs) which initiate the innate immune response (Jassam et al., 2017; Alam et al., 2020). DAMPs include ATP, alarmins, S100 proteins, high-mobility group box 1 (HMGB1) and can be detected by the astrocytes via a variety of Toll-like receptors (TLR) as previously reviewed (Sofroniew, 2020). Similarly, stressed or dying astrocytes can also produce DAMPs and alarmins which activate resident CNS macrophages (microglia) and peripheral macrophages in order to clear cellular debris (Burda et al., 2016; Alam et al., 2020). For example, nuclear alarmin IL-33 is released from damaged oligodendrocytes in white matter and in grey matter astrocytes at 1 day following spinal cord injury (Gadani et al., 2015). Primary astrocytes obtained from injured mice showed secretion of monocyte-attracting chemokines such as CCL2 and CXCL10 in response to IL-33.

Astrocytes are able to detect mechanical shear forces associated with trauma via activation of mechanoreceptors, allowing rapid influx of extracellular Ca^{2+} and Na^{+} into astrocytes (Fig. 4B) that induces a "reactive state" and ATP release via connexin semi-channels (reviewed in (Burda et al., 2016)). Extracellular ATP further activates the surrounding astrocytic network and contributes to the recruitment of microglial and immune cells to the injury site (Fraunberger and Esser, 2019). Astrocytes detect ATP via purinergic receptors P2X7 and P2Y1R expressed on their end feet (Talley Watts et al., 2013). These receptors contribute to brain edema formation and release of pro-inflammatory cytokine IL-1β by astrocytes in response to CCI in mice (Kimbler et al., 2012). ATP signaling mediates astrocyte reactivity after TBI and inhibition of P2X7 improves neurobehavioral outcomes. Additionally, ATP released by astrocytes and other damaged cells mediates chemotaxis in microglia, activating the motility of microglial processes to the lesion site (Davalos et al., 2005; Wu et al., 2007).

Cross-talk between astrocytes and microglia via interaction and coordination between these two glial cell types in the context of neuroinflammation are mediated by secretion of cytokines. (Jha et al., 2019; Vainchtein and Molofsky, 2020). After brain injury, astrocytes activate microglial responses and *vice versa* but data are sparse and exact mechanisms remain unknown for the pediatric brain (reviewed in (Mira et al., 2021)). During healthy neural circuit development, astrocytes directly promote microglia phagocytosis and synapse engulfment by secreting a nuclear alarmin IL-33 (Vainchtein et al., 2018), but knowledge of astrocyte-microglia interactions in pediatric brain disorders is underdeveloped. Classically, microglia have been seen as the primary driver of changes in astrocytes with a larger literature showing, in adult brain or *in vitro*, the effects of activated microglia on astrocyte properties. For example, LPS-activated microglia inhibit astrocytic phagocytosis by secretion of TNF-α, IL-1α and complement component subunit 1q (C1q) and thus contribute to neurotoxic astrocytic capacities *in vitro* (Liddelow et al., 2017). In addition, microglial cells act on developing astrocytes, as microglial-conditioned medium increased the percentage of cells positive for GFAP *in vitro* (Nakanishi et al., 2007). Thus, IL-6 and leukemia inhibitory factor (LIF) released by activated microglia promote astrocytic differentiation via the activation of the JAK / STAT and MAPK pathways (Nakanishi et al., 2007). In response to neuronal damage induced by CCI in adult brain, microglia release IL-6 via HMGB1/TLR4 signaling (Laird et al., 2014). Interleukin-6 is recognized by its receptor IL-6R on astrocytes and leads to up-regulation of AQP4 expression, reactive astrocyte formation and consequently the promotion of edema (Laird et al., 2014). In case of pediatric brain trauma, mechanisms of interaction between astrocytes and microglia are unknown and deserve to be identified in future studies.

The capacity of astrocyte to secrete various substances (VEGF-A, IGF-1, retinoic acid etc.) modulates the blood-brain interface status. This can contribute to the recruitment of immune cells, as well as to the interaction with the immune system (Han et al., 2021). Astrocytes are thus key players in inflammatory responses triggered by brain trauma. They can produce and secrete immunomodulatory anti- and pro-inflammatory mediators like cytokines and chemokines which are involved in the innate immune response and modulate the neurovascular unit (Weiss et al., 1998; Szmydynger-Chodobska et al., 2010; Choi et al., 2014; Alam et al., 2020; Sofroniew, 2020). Cytokines and chemokines could have both neurotoxic and neuroprotective roles at the lesion site. Cortical astrocytes produce chemokine (C-X-C motif) ligand 1 (CXCL-1) and chemokine (C-C motif) ligand 2 (CCL2) in a rat CCI model at 6 h post impact, which is associated with an influx of inflammatory cells (Szmydynger-Chodobska et al., 2010). Mild TBI in adult rat FPI model up-regulates the levels of TGF-β1 in blood, cortex tissue and CSF

(Patel et al., 2017). This cytokine can potentially be released by astrocytes and increase the permeability of BBB via effects on claudin-5 (Constam et al., 1992; Shen et al., 2011). Importantly, TGF-β1 levels peak in the CSF in adult patients with severe TBI on the first day of injury (Morganti-Kossmann et al., 2009). The role of TGF-β1 in pediatric TBI patients remains unknown. A recent study showed that human astrocytes secrete IL-6 in response to shear stress *in vitro* (Khodadadei et al., 2021). Following trauma, astrocytic NF-κB pathway is activated allowing the production of IL-6, TNFα, IL-1β and metalloproteases (MMP-9) (Szmydynger-Chodobska et al., 2010; Pan et al., 2012; Zhou et al., 2021). Levels of a key pro-inflammatory cytokine IL-1β increase after TBI in human patients (Yue et al., 2019) and in rodent models (Kamm et al., 2006; Clausen et al., 2019; Zhou et al., 2021). The so-called "inflammasome" is a large intracellular multiprotein complex allowing the secretion of cytoplasmic IL-1β and IL-18 via the activation of caspase-1 (Kerr et al., 2018). Adult TBI patients have elevated levels of inflammasome-associated proteins such as IL-18, caspase-1 and ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) in serum and cerebrospinal fluid (Adamczak et al., 2014; Kerr et al., 2018). Closed-head injury is also associated with a release of IL-18 both in humans and rodents (Yatsiv et al., 2002). Recent data suggest that inflammasomes are present not only in neurons (de Rivero Vaccari et al., 2009), microglia and infiltrating macrophages, but also in astrocytes. Human astrocytes express a functional inflammasome which consists of NLRP2 (NACHT, LRR and PYD domains-containing protein 2), caspase-1 and ASC (Minkiewicz et al., 2013). NLPR2 inflammasome activation by ATP contributes to the maturation of pro-IL-1β and its secretion as part of an astrocytic innate immune response. Reactive astrocytes express NLRC3 and NLRC4 inflammasome (NLR family caspase recruitment domain (CARD)-containing protein 3 and 4, respectively) in both mice and patients with demyelinating disease (Freeman et al., 2017). Absent in melanoma 2 (AIM2) inflammasome and caspase-3 were activated in astrocytes in the spinal cord from mice with induced multiple sclerosis (Barclay et al., 2022). This AIM2 inflammasome activation was astrocyte specific as microglia showed no inflammasome activation. Only very few data exploring the role of astrocytic inflammasomes in TBI models are currently available and this topic requires further investigation (Liu et al., 2013; Brickler et al., 2016). Brain injury activates the NLRP3-inflammasome in astrocytes along with neurons and microglia in adult rats in an adult WD model (Liu et al., 2013). Inflammasome proteins (NLRP3, ASC and caspase-1) were colocalized with GFAP-positive astrocytes in peri-contusional cortex 3 days after injury.

In line with the paracrine role of astrocytes in pathological situations, a recent hypothesis proposes that astrocytic microRNAs contained in extracellular vesicles (exosomes) could regulate gene expression in neighboring cells and thus modulate immune response (reviewed in (Lafourcade et al., 2016)). Mouse primary astrocytes release exosomes containing 135 different microRNAs after application of brain extract from adult TBI mice, which promote an anti-inflammatory phenotype in primary microglia suggesting a new mode of astrocyte-microglia cross-talk (Long et al., 2020). Moreover, treatment with microRNA (miR-873a-5p), highly enriched in astrocytic exosomes, inhibited NF-κB pro-inflammatory pathway in adult mouse CCI model leading to reduced cortical lesion area, attenuated edema and improved neurological outcomes during 2 weeks post injury. Along with reciprocal communication between microglia and astrocytes (Vainchtein and Molofsky, 2020), there could be a common synchronous response in both glial cell types, induced by the same factors. Altogether, these findings suggest the importance of cross talk between the astrocyte and microglia cells as part of a potentially coordinated innate immune response after perturbations to brain homeostasis.

4. Concluding remarks

It is clear that astrocytes are an integral and essential part of innate immune response triggered by brain trauma, as they detect tissue damage and rapidly respond to injury by releasing numerous cytokines, chemokines and growth factors. The rapid astrocytic immune response to TBI is due to the presence of inflammasomes in astrocytes, but requires further confirmation. Several lines of evidence indicate that astrocytes interact with immune-competent cells (cross-talk with microglia) and recruit peripheral immune cells to the lesion site. Reactive astrocytes have the capacity to regulate the neuro-vascular unit in response to brain trauma. The mechanisms of communication of astrocytes with surrounding cells (release of exosomes, ATP, growth factors, cytokines and chemokines) in order to coordinate response to injury need further investigation using pre-clinical brain trauma models.

The immunological abilities of astrocytes highlighted in this review should be explored in the context of pediatric TBI, as very few studies have focused on neuroinflammation in the developing brain (Fraunberger and Esser, 2019). Little is known about the capacity of immature astrocytes to secrete cytokines/chemokines and to interact with immune cells during acute phase of pediatric TBI. Another open question would be that of astrocytic "molecular immunological memory" of inflammatory conditions happening early in life. Do astrocytes keep a specific molecular signature, acquiring a primed or sensitized state, after a neuroinflammatory response linked to brain trauma (Cunningham et al., 2019)? If yes, another question would be for how long astrocytes could stay primed? Finally, there are remaining questions as to how this eventual "immunological memory" of astrocytes could impact cognitive functions and susceptibility to neurodegenerative or depressive-like conditions later in life? A better understanding of the immune role of astrocytes is particularly relevant for the TBI in children with following key questions summarized in Table 2. Further translational studies would facilitate therapeutic solutions for pediatric TBI patients which are currently lacking to improve recovery rate and offer a better quality of life.

Authors contributions

PEP, LH, JPK and JB have contributed to the conception, the writing of the paper and approved the submitted version. PEP and LH have drafted the Fig. 3 and 4 using Biorender. JB have drafted the Fig. 1 and 2 using Biorender.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

Table 2
Some outstanding questions on the role of astrocytes in pediatric TBI.

	Question:
1	Do all astrocyte sub-populations respond equally to injury in adult and pediatric TBI? Is there one specifically defined astrocyte sub-population actively responding to the injury?
2	Does similar heterogeneity of astrocyte populations exist in the context of pediatric TBI?
3	Are cellular and molecular mechanisms similar after TBI in adult and developing brain?
4	Do the changes in astrocyte properties impact the brain development and maturation of the brain circuitry? And how?
5	Are there functional differences between astrocytic response to the TBI between different species?
6	How do astrocyte changes differ between brain regions after TBI in adult and pediatric patients?
7	Immunological properties of astrocytes have been proposed in preclinical models of immune challenges. Do immature astrocytes play an immune function after pediatric TBI?
8	How do pediatric "reactive" astrocytes evolve over the time and in the different brain regions after the injury? Do the reactive astrocyte keep an immune memory for future brain injuries?

Data availability

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

Acknowledgments

We acknowledge Drs Christophe Dubois, Andre Obenaus and Klaus G Petry for their expertise and helpful discussions.

This work was supported in part by NINDS, USA grant R01NS11960 (JB); ANR-Nanospace (JB), Eranet Neuron ANR Neuvasc (JB), Eranet neuron ANR MISST (JB).

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