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Review

Pathophysiology of the choroid plexus in brain diseases

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Abstract. The choroid plexus, located in the ventricular system of the central nervous system (CNS), obtains numerous roles critical for the proper development and operating of the CNS. The functions range from the best-known ones of the barrier and cerebrospinal fluid (CSF) producer, through participation in immune answer, 'nourishment, detoxification and reparation of the rest of the CNS. Increase number of studies point out the association between choroid plexus dysfunction, characterized by alterations in secretory, transport and barrier capabilities, and the broad spectrum of clinical conditions, as well as physiological aging. We present a brief overview of pathological states known or speculated to be connected to choroid plexus dysfunction, ranging from neurodevelopmental, to autoimmune and neurodegenerative diseases. We also cover the topic of choroid plexus tumors, as well explained involvement of the choroid plexus in pathogen invasion of the CNS, also referring to the currently actual SARS-CoV-2 infection. Finally, we have also touched conducted studies on the choroid plexus regenerative potential. With the information provided in the review we want to point out the importance and call for further research on the role of the choroid plexus in the sustainability of central nervous system health.

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; BBB, blood-brain barrier; BCSFB, blood-cerebrospinal fluid barrier; CP, choroid plexus; CPECs, choroid plexus epithelial cells; CPe, choroid plexus epithelium; CSF, cerebrospinal fluid; ICP, intracranial pressure; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NO, nitric oxide; TJs, tight junctions.

Introduction

The choroid plexus (CP) is a dynamic, highly vascularized secretory structure present in all four ventricles of the brain (i.e. laterals, third, and fourth), and thus strategically located to connect the peripheral blood circulation and the central nervous system (CNS) (Lun et al. 2015; Simon and Iliff 2016). The CP obtains multiple functions, essential for the maintenance of the CNS' proper functioning and homeostasis (Redzic and Segal 2004; Ghersi-Egea et al. 2018; Johanson 2018).

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The tissue is composed of vessels penetrating stroma, surrounded by a single layer of cuboidal choroid plexus epithelial cells (CPECs), forming choroid plexus epithelium (CPe) (Emerich et al. 2005; Simon and Iliff 2016). The CPECs are tightly sealed by tight junctions into the blood-cerebrospinal fluid barrier (BCSFB). The BCSFB, together with anatomically similar blood-brain barrier (BBB), situated at the level of cerebrovascular endothelium, prevents the free paracellular entrance of blood-borne substances (Redzic 2011; Lauer et al. 2017), and thus supports the maintenance of the brain's milieu. Unlike in the BBB, endothelium of the CP is fenestrated (Wolburg and Paulus 2010; Lun et al. 2015; Simon and Iliff 2016), representing an important physiological basis for the CSF production (Cserr et al. 1992; Lun et al. 2015), as enabling ion and water transport (Fig. 1). The permeability

of the layer is modulated by surrounding pericytes (Saul et al. 2020). Both layers, the CP endothelium and epithelium, lay on the basal lamina (Wolburg and Paulus 2010). It is proposed that this extracellular matrix play an important part in the organization and maintenance of the BCSFB integrity (Vandenbroucke et al. 2012).

The CPECs have an apical border (i.e. formed of microvilli and incorporated cilia) and basolateral interdigitations (i.e. in some publications referred to as basolateral labyrinth), significantly increasing the surface of the tissue and creating polarity of the layer (Lauer et al. 2017). Cilia support the CSF movement (Narita and Takeda 2015). Large mitochondrial content supports extensive transport and secretion properties of the CP (Spector et al. 2015). Under normal conditions, the mature CPECs do not undergo replacement or degeneration (Liddelow et al. 2010). The CPECs share the same origin with ependymal cells, lining the CSF-filled ventricular space (Wolburg and Paulus 2010)

Tight junctions (TJs), adherens junctions, and gap junctions are protein junctional complexes participating in the establishment of cell-cell adhesion and functional BCSFB within the CPe (Tietz and Engelhardt 2015; Solár et al. 2020b). Among these three groups, the TJs are located the most apically, and include occludin, claudins, and junctional adhesion molecules (JAMs). Their apical distribution is maintained through interactions with the actin cytoskeleton (Campos et al. 2016). Claudins reported in the CPe are Clauidn-1,-2,-3,-11 (Wolburg et al. 2001; Steinemann et al. 2016). TJs are prone to degradation by the activities of matrix metalloproteinases, probably infringing barrier integrity (Kirchner et al. 2000; Yang et al. 2007). The BCSFB shows functionality already in the early developmental stages (Dziegielewska et al. 1979; Møllgård et al. 1979).

The CP is 'the number one' CSF producer (Cserr et al. 1992; Redzic et al. 2005), while the sources of rest, with still poorly defined contribution, are brain interstitial fluid, ependyma and capillaries (Sakka et al. 2011). The CSF production at the CP is occurring through a series of well-organised transfers of water and ions *via* bidirectionally deployed transporters on the CPs. Such polarized distribu-

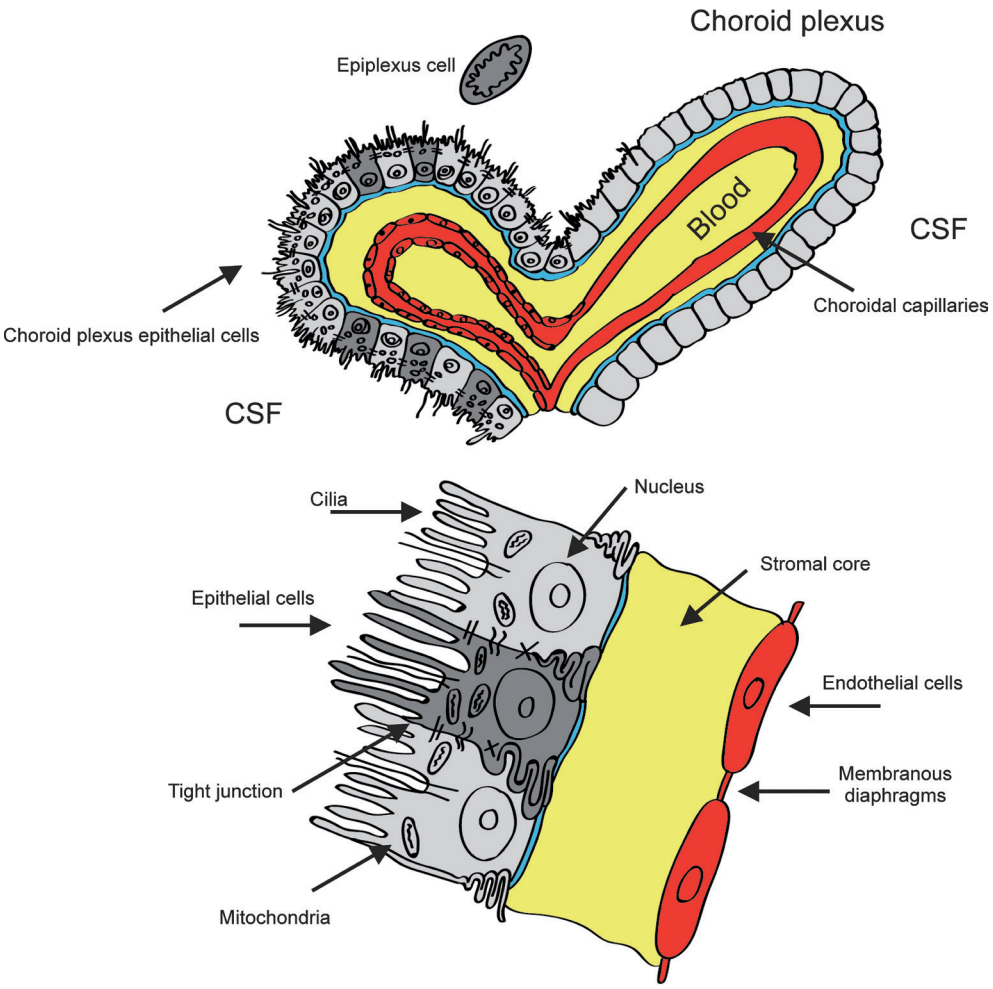

Figure 1. Structure of the choroid plexus. The choroid plexus is a highly vascularized secretory structure present in all four ventricles of the brain. The tissue comprises vessels penetrating stromal space, surrounded by a single layer of cuboidal choroid plexus epithelial cells (upper panel). Tight junctions tightly seal the choroid plexus epithelial cells (CPEC) into the blood-cerebrospinal fluid (CSF) barrier. The monolayer of CPEC surrounds the stromal core and capillaries. In contrast to the brain's parenchyma, the capillaries of the choroid plexus are fenestrated. The individual endothelial cells are connected by thin membranous diaphragms that are permeable to small molecules and water (bottom panel).

tion of transporters is defined and supported by specific cytoskeleton arrangements (Damkier et al. 2013). By traditional theories of the CSF dynamics, the CSF produced in the ventricles, further enters and circulates in subarachnoid space surrounding the brain and spinal cord, where it gets reabsorbed into venous blood (Redzic and Segal 2004; Lun et al. 2015; Simon and Iliff 2016; Bothwell et al. 2019). These theories are expended with new knowledge about the existence of the glymphatic system within the brain parenchyma, in which the CSF that has exited subventricular circulation, further picks up the waste products from brain tissue, that are being drained into the lymphatic system (Verkhratsky et al. 2015). Circulating around the brain, the CSF mechanically protects it, and also helps in the maintenance of the normal intracranial pressure (Spector et al. 2015). Additionally, *via* the CSF, the CP 'nourishes' the brain with vital components for its development and maintenance in adulthood, that is being produced by the tissue itself, or transported across it (Emerich et al. 2005; Lehtinen et al. 2013; Johanson 2018). Although being filtrates of plasma, these two bodily fluids differ in pH, the concentration of protein, amino acids, and ions (Damkier et al. 2013; Hladky and Barrand 2014). The CP tightly regulates the CSF composition, and physiological rates of production (Nilsson et al. 1994; Sakka et al. 2011; Damkier et al. 2013; Spector et al. 2015; Pardridge 2016), and their changes are usually associated with neurological states and the CP's dysfunction (Reiber 1994, 1995; Simon and Iliff 2016). For example, disruption of the CP barrier leads to leakage of the unwanted proteins from plasma osmotically followed by water influx, changes in the regional CSF flow, inflammation and neural damage, especially affecting subventricular regions, i.e. hippocampus (Johanson 2018).

Acting as the immune gate, the CP very actively participates in the establishment of the immune response within the CNS in health and disease (Engelhardt and Ransohoff 2012; Ghersi-Egea et al. 2018). CP stroma harbours macrophages and dendritic cells, while on the CSF-facing surface are attached Kolmer's epiplexus cells, all being attributed with antigen-presenting properties (Lauer et al. 2017). During neuroinflammation, the CP serves as a niche for T cell infiltration. Inside the CP's stroma, being presented with antigen by APCs, CD4+ T cells undergo activation and proliferation, and further shape CNS response (Strominger et al. 2018). The stimulus can upregulate the expression of chemokines in the CPECs. As the first line of the CNS defence, the BCSFB properties, as well as the proinflammatory and anti-inflammatory profile of the tissue, change upon peripheral inflammatory insult (Emerich et al. 2005; Marques et al. 2009).

The CP and the CSF perform a significant role in the detoxification of the brain from metabolic wastes, potentially toxic compounds, and drugs. The CP owns a mechanism for impeding entrance and bio-distribution of noxious compounds and drugs within the brain *via* its machinery of metabolizing enzymes (Ghersi-Egea and Strazielle 2001; Crossgrove et al. 2005; Iliff et al. 2012).

Besides neurogenic capabilities of the CP tissue itself (Itokazu et al. 2006; Prasongchean et al. 2015), the CP might support neurogenesis of the other parts of the CNS as well, through secretion of various neurotrophic factors (Borlongan Cesar et al. 2004). So for example, by 'tuning' the CSF composition, the CP affects properties of the subventricular zone, an important neural source of the adult brain (Falcao et al. 2012).

Systemic inflammation

Experimentally, systemic inflammation is usually provoked by intravenous/intraperitoneal injection of LPS (Dickson and Lehmann 2019; Solár et al. 2020b). Response to this peripheral stimulus in the CP includes changes in anti- and pro-inflammatory profiles, down-regulation of TJ proteins, and proteins of extracellular matrix involved in cell-to-cell interactions, indicating the BCSFB destruction. In response to the adverse effect of proteases and matrix metalloproteinases (MMPs), which are likely to occur in the midst of barrier damage, increase production of inhibitor metalloproteinase 1 was observed at the CP, as a possible protective mechanism of the CP for tissue itself (Flannery 2006; Marques et al. 2009; Dickson and Lehmann 2019). Additionally, lipocalin 2, a protein whose bacteriostatic effects have been shown *in vitro* and *in vivo*, has found to be upregulated for 72 h during acute infection in the CP, and so likely, the CP also protects the rest of the brain from spreading of infection (Marques et al. 2009).

Systemic inflammatory syndrome, is a highly mortal systemic inflammatory condition, significantly effecting the brain. The depletion or inhibition of MMP8 has a protective effect from death and neurological complications of the disease, probably through the prevention of BCSFB leakage correlating with increase CSF cytokine levels, brain inflammation, and downregulation of the brain glucocorticoid receptor (Vandenbroucke et al. 2012) . A similar effect of broad-spectrum of MMP inhibitors was also shown *in vitro* (Zeni et al. 2007).

Aging, Alzheimer's disease and other neurodegenerative disorders

Changes in the neurovascular unit are well described (Zlokovic 2008; Sweeney et al. 2018). In addition, there is a growing number of studies indicating that morphological and functional alterations of the CP play a significant role in the pathology and progression of neurodegenerative disorders, as well as in physiological aging. **Alzheimer's disease** (AD),

the most common form of dementia, is histopathologically characterized by extracellular amyloid plaques (formed of Aβ peptides), and intracellular neurofibrillary tangles, formed of microtubule-associated tau protein (Balusu et al. 2016; Kent et al. 2020; Alzheimer's Association 2021). Their presence has been driven into connection with progressive cognitive decline and brain atrophy, and decreased CSF turnover (Nelson et al. 2009; Smolek et al. 2016; Mormino and Papp 2018; Attier-Zmudka et al. 2019; Jadhav et al. 2019).

Already in 1997, Hampel and colleagues speculated that alterations of the BCSFB may contribute to AD pathology (Hampel et al. 1997). The pattern of morphological and functional changes of the BCSFB in aging and AD is very similar, but significantly accelerated in the latter, which to some extend supports the theory of AD as 'amplified senescence' (West et al. 1997), therefore, through the chapter, they will be discussed in parallel. At the level of epithelium, there is cell flattening, along with the shortening of microvilli, irregular shaping of nuclei and common presence of lipid vacuoles (Serot et al. 2001; Kaur et al. 2016). Underneath the epithelium, the basal membrane gets thicker too, as well as tissue stroma, while the basal membrane of endothelium is seen moderately increased and becomes fragmented (Preston 2001; Serot et al. 2001; Emerich et al. 2005). In the cytoplasm of the CPECs can be observed inclusions such as Biondi bodies (Kiktenko 1986; Wen et al. 1999; Balusu et al. 2016); psammoma bodies (Wen et al. 1999; Jovanović et al. 2010; Raha-Chowdhury et al. 2019), and lipofuscin (Wen et al. 1999; Krzyzanowska and Carro 2012).

An increase of nitric oxide (NO) levels interferes with immune cell trafficking across the BCSFB (Baruch et al. 2015); and immune gate function can be restored by implementing NO scavengers through induction of the NF_kB/p65 pathway. Analyses of autopsied CP showed increased levels of heat shock protein HSP90 (Johanson et al. 2004). Disruption of the barrier may occur even before the development of AD pathology, as based on measurements of CSF/serum albumin ratio and CSF secretory Ca^{2+}-dependent phospholipase A2 activity (Chalbot et al. 2011).

Characteristic increased Aβ levels in the CSF in AD, whose presence has been linked to cognitive decline (Wu et al. 2016), probably come as a result of an imbalance between production and clearance of Aβ peptides (Hardy and Selkoe 2002; Mawuenyega et al. 2010). There is also a load of these peptides in the CPECs, probably resulting in decreased CSF production and Aβ clearance leading to upregulation of pro-inflammatory molecules (IL1, IL6, TNFα and iNOS) and increased levels of MMPs, that both may lead to barrier alterations (Eriksson and Westermark 1986; Dietrich et al. 2008; Wolburg and Paulus 2010; González-Marrero et al. 2015; Brkic et al. 2015b). It is speculated that mitochondrial dysfunction present in the AD CP, may be attributed at least partly to Aβ overload within the tissue (Krzyzanowska and Carro 2012). Furthermore, toxic Aβ load can be caused by down-regulation of proteins involved in Aβ peptide clearance, like transthyretin (Serot et al. 1997; Chen et al. 2005; Van Cauwenberghe et al. 2020), megalin (Carro et al. 2005; Alvira-Botero and Carro 2010), and clusterin (Zlokovic et al. 1996), as observed in AD. Removal of Aβ peptides from the CNS happens through the joined actions of the brain barriers, who share the common transporters for this peptide, but can show different expression profiles in the disease. In AD, the expression of efflux transporter lipoprotein receptor-related protein 1 in the CP is upregulated, while influx transporter lipoprotein receptor-related protein 2 is downregulated, which is in contrast to changes observed on the BBB, indicating coordinated clearance activities between barriers, and that the BCSFB may serve as potential back-up mechanism of the BBB malfunctioning (Pascale et al. 2011). Levels of LPS, are present in aging and AD, and co-localize with amyloid plaques (Zhan et al. 2018). Interestingly, the Aβ burden exists in 20% cognitively normal individuals (Rodrigue et al. 2012).

Besides a decrease in clearance potential creating toxic protein load, changes in the structural integrity of the CP probably lead to the decrease of secretory activities and diminished brain supply with necessary compounds. Alterations in the expression of genes involved in CSF production have been reported in AD patients (Kant et al. 2018). Abnormalities in the CSF secretion and turnover have been observed in human and animal models of aging (Silverberg et al. 2001; Redzic et al. 2005). The estimated 0.2 ml/h level of CSF production in AD patients, is remarkably lower than the normal rate (Silverberg et al. 2010). In AD, there is an increase in vasopressin binding sites on the CP, which can decrease blood flow into the CP and reduce the CSF production (Faraci et al. 1990; Korting et al. 1996).

Both aging and neurodegenerative disorders are of inflammatory nature (Tarkowski et al. 2003; Simen et al. 2011; Zilka et al. 2012; Brkic et al. 2015a; Kinney et al. 2018). Baruch et al. (2014) showed that the CP expresses a unique 'aging signature', mainly through the type I interferon signalling by IFN-γ, that chronically upregulates in aging. Blocking of this pathway resulted in partial restoration of aging-disturbed cognition and hippocampal neurogenesis. Interplay, which is a diverse pattern of changes in the expression of INF-I and INF-II signalling, observed in aging and AD, maybe a potential therapeutic target to slow aging and prevent AD (Baruch et al. 2014; Mesquita et al. 2015). Additionally, the CP has high expression of the KLOTHO gene, coding for 'anti-aging' hormone present in the blood and the CSF, that has shown effects against AD pathology and cognitive impairment (Liddelow 2015; Zeng et al. 2019). AD patients have decreased levels of this hormone in their CSF (Semba et al. 2014). Ott et al. (2010) examined the relationship between changes in ventricular volumetry and CSF biomarkers in mild-cognitive impaired

and AD patients. Although, they found a strong relationship between Aβ levels and neuropathology of AD, characterized also with hydrocephalic enlargement, the relation between volumetric changes and the CSF biomarkers was not significant, and authors debate that possible reasons for the results might 'hide' in alterations of the brain barriers and decrease of the CSF production with aging and in neurodegeneration.

The hallmark of the second most common neurodegenerative disorder, **Parkinson's disease** (PD), is pathological α-synuclein (α-Syn). The α-Syn accumulates and aggregates, disturbing synaptic functionality and mitochondrial energy production, which is manifested in motor impairment and cognitive decline (Bates and Zheng 2014; Bridi and Hirth 2018). There is still a rather scarce number of studies on the connectivity between the BCSFB functioning/alterations and neurodegeneration in PD. Bates et al. (2015) showed that α-Syn can be transported *via* the BSFB monolayer, and that there is a significant increase of α-Syn uptake by the CPECs after exposure to manganese (i.e. toxic metal implicated in PD onset). Increased albumin transfer *via* the BCSFB that occurs in advanced stages of the disease, indicates the barrier's disruption (Pisani et al. 2012). The effect of neurotrophins derived from encapsulated porcine CPECs (termed NTCELL) considered to be a promising regenerative treatment option in PD, is still under testing for efficiency, but the phase II study, did not show improvement in tested subjects (Snow et al. 2019). Very similarly, encapsulated rat CP cells were tested for regenerative treatment in another neurodegenerative disorder, **Huntington disease** (HD), but here the transplants showed a neuroprotective effect, with variations among different neuronal populations (Borlongan et al. 2007). Genomic studies of post-mortem CP isolates revealed up-regulation of cadherin and down-regulation of Cl-5 in this disease group patients (Stopa et al. 2018).

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting mostly motor neurons, especially the one of the brain and spinal cord, in which improper accumulation of neurofilaments occurs (Smith et al. 2015; Saul et al. 2020). Potential mechanisms of disease spread are neuroanatomical propagation and the factors circulating the CSF (Ravits 2014; Smith et al. 2015). Significant increase of total protein (Leonardi et al. 1984) and complement component 3c concentrations (Annunziata and Volpi 1985) correlating to the CSF albumin/serum albumin ratio, as well as an increase of blood-borne substances (Donnenfeld et al. 1984) in the CSF of ALS patients indicate probable barriers disruption (Garbuzova-Davis and Sanberg 2014). The CP probably fails to help in fighting inflammation present in disease, as the mouse model of ALS (mutant $SOD1^{G93A}$) and shows the decrease in IFN-γ singling needed for CD4+ recruitment *via* the CP (Kunis et al. 2015). Saul et al. (2020) have reported a wide range of histopathological and transcriptomic changes in post-mortem CPs of ALS patients evident through alteration/downregulation of tight junctional proteins, and mislocation and/or overall or regional loss of some of them, as well as probable disruption of vascular integrity (i.e. downregulation and discontinuous expression of CD31) and pericytes reduction around the vessels. These CP alterations may result in decreased clearance potential and previously mentioned changes in the CSF composition. An increase number of macrophages, C-reactive protein (CRP) and MerTK receptor tyrosine kinase positive cells, witness ongoing inflammation and apoptosis in the tissue. Interestingly, expression of measured MMPs was downregulated.

Hydrocephalus and the CP tumors

Hydrocephalus

Hydrocephalus is a condition characterized by ventricular enlargement (i.e. ventriculomegaly), increased CSF volume and usually intracranial pressure, that in the case untreated, can be life-threatening (Grote and Hassler 1988; Liptak 2007; Kahle et al. 2016; Karimy et al. 2016). Still, correlations between the intracranial pressure (ICP) and CSF formation in hydrocephalus can vary (Calhoun et al. 1967; Lorenzo et al. 1970). Division of the disease made by Damkier et al. (2013), classifies it based on time of appearance throughout life (i.e. infantile, juvenile, adult forms), the effect on ICP (i.e. high- and normal-pressure), the way of CSF flow, that is if there is a free flow from ventricles towards subarachnoid space (i.e. communicating and non-communicating form), and progression of the disease (i.e. active and arrested form).

The disease arises due to some kind of perturbation in regular CSF flow that is either result of its obstruction, increase, or decrease in the CSF flow (Oi 2011) and can be caused by a variety of disorders like, infections, tumors, hemorrhage, and strokes (Krishnamurthy and Li 2014) leading to further clinical complications.

Morphological-functional effects of hydrocephalus on the CP tissue include atrophy of epithelium, reduction in number, as well as shortening and swelling of microvilli, sclerotic stroma, dilatation of intracellular spaces and of basolateral interdigitations (Shuangshoti et al. 1965; Madhavi and Jacob 1995; Owler et al. 2010). Intercellular junctions seem to be preserved (Tirapelli et al. 2007). The changes are accompanied by infestation and the increase of various types of immune cells (Go et al. 1976; Lu et al. 1996; Solár et al. 2020a). The rate of proliferation increases . Also, mutations in *Mpdz*, one of only eight genes associated with heritable hydrocephalus, coding for eight junctional proteins, are associated with pronounced permeability of the BCSFB, and probably a subsequent enormous increase of the CSF protein

concentration for even 53-folds (Yang et al. 2019). When ICP increased, seems that the CP has protective mechanisms for regulation of CSF flow to decrease the pressure (Knuckey et al. 1993; Faraci et al. 1994). Normally present diffused dispersion of aquaporin-4 in the cytoplasm of the CPECs (Speake et al. 2003), may allow reabsorption of water from the CSF back into capillaries and be the compensatory mechanism of the cell against hydrocephalus, while the relocation of AQP1 inside the cytoplasm, may be happening in the same goal (Speake et al. 2003; Owler et al. 2010). Dohrmann (1971) for the first time connected morphological changes in the CP with changes in the CSF pressure. In dogs with experimentally provoked hydrocephalus flattening and compacted cytoplasm of the CPECs were observed, as probable results of increased intraventricular pressure, and ventriculojugular shunt restored these morphological alterations already after one day of the procedure. Several groups have demonstrated that cilia defects at the CPECs can cause communicating hydrocephalus (Banizs et al. 2005; Wodarczyk et al. 2009; Tissir et al. 2010; Swiderski et al. 2012; Liu et al. 2014; Narita and Takeda 2015).

The ventricular shunt is still the predominant surgical treatment of hydrocephalus but also other treatments involving manipulations in the ventricular system have shown great success (Warf 2005, 2013; Norkett et al. 2016). Of pharmacological approaches, positive and promising results in a decrease of CSF production have come from the use of acetazolamide, an inhibitor of carbonic anhydrase and exendin-4 (Carrion et al. 2001; Ivkovic et al. 2015; Bothwell et al. 2019).

CP tumors

CP tumors, present as neuroepithelial neoplasms are rare, and mostly present in childhood accounting for 2–5% of brain tumors in children (Rickert and Paulus 2001; Merve et al. 2019). In that age group they are mostly found in lateral ventricles, and if occur in adulthood, they mostly affect the fourth ventricle (Hasselblatt et al. 2009; Lun et al. 2015). CP tumors can be divided into benign tumors, i.e. papillomas and carcinomas whose pathological findings range from well-preserved structures in both, papillomas and carcinomas, to severely disturbed tissue morphology (McComb and Burger 1983). Still, certain differential markers for distinguishment between these two tumor types exist (Solár et al. 2020b). Also, carcinomas are characterized by loss of aquaporin-1 expression (Longatti et al. 2006). High expression of twist-related protein 1 in the CP papillomas, as well as glial fibrillary acidic protein in both tumor types (Rickert and Paulus 2001), indicates a high proliferation rate within disease tissue. The clinical picture often indicates hydrocephalus, accompanied by increased ICP (Rickert and Paulus 2001; Lin et al. 2019). Merve et al. (2019) have created a mice model of a human benign CP tumor with overexpression of c-Myc, the protein of the MYC family involved in numerous cell processes (i.e. proliferation, apoptosis, metabolism), and that is often overexpressed in tumors. The group has linked c-Myc overexpression with inflammation in the tissue, presented by increased infiltration of CD3+T-cells (i.e. especially CD4+T-helper cells) and CD68+ macrophages, opening the possibility of anti-inflammatory therapy of the CP tumors.

Autoimmune disorders

Studies on **multiple sclerosis** (MS)**,** the most prevalent CNS inflammatory disease, characterized by inflammation, demyelination, and neurodegeneration, have provided many answers about brain-immune interactions (Vercellino et al. 2009; Martin et al. 2016). The clinical picture shows a brain with lesions, that have both infiltrations of helper (CD4+) and cytotoxic (CD8+) T cells (Reich et al. 2018), of which the first subtype significantly exceeds the number of the second indicating the central role that CD4+T cells hold in MS pathology (Rangachari and Kuchroo 2013). An experimental model of disease, experimental autoimmune encephalomyelitis (EAE) significantly affecting the CP morphology and provoking immunological answers in the CP epithelium and stroma (Frausto et al. 2007). During EAE, the CP shows upregulation of adhesion molecules, chemokines, statins, and interleukins, supporting infiltration of peripheral autoregressive immune cells (Engelhardt et al. 2001). VCAM-1 possibly plays a role in leukocyte transmigration in MS, as patients show VCAM-1 upregulation in the CPe (Vercellino et al. 2008). Murugesan et al. (2012) have analysed the difference of immune answers between the CP stromal capillary and the CP epithelium in response to MOG_{35-55} peptide immunization. While the stromal capillary showed increased expression of CCL5, CCL19, and the endothelium showed upregulation of C3, CXCL10, CCL19 and selectin. Both tissue constituents showed upregulation of Bm2 and C3. Also, the CSF of MS patients shows higher abundancy in immune cell content in comparison to control, indicating an increase immune cell crossing of the BCSB (Han et al. 2014).

IL-17 producing effector T helper cell subpopulation, Th17 cells, is associated with the onset of EAE (Korn et al. 2009). The cells gain access *via* the CP through chemokine receptor CCR 6 and chemokine ligand CCL20, constitutively expressed in the CPECs, that is being upregulated on IL-17 stimuli (Reboldi et al. 2009; Kaur et al. 2013). Kuwabara et al. (2017) speculated the importance of CCL19/CCL21-CCR7 ligand in the generation of Th17 subset *via* IL-23, but it was later proved that initial differentiation of Th17 cells is mediated by cytokine combination of TGF-β and IL-6 (Rangachari and Kuchroo 2013). The entrance

of autoaggressive T cells further provokes characteristic demyelination and neuronal loss within the brain (Dixon and Pérez 2020).

Human post-mortem CP tissue studies showed a significant increase of CD4+ and CD8+ T cell populations and granulocytes (mostly neutrophiles) in MS patients, with a great abundancy of MHCII-expressing macrophages and DC cells (Rodríguez-Lorenzo et al. 2020).

As far as structural changes in the tissue during the disease, swelling of CP stromal capillaries probably as a result of increased capillary permeability (Murugesan et al. 2012) and changes at the level of microvilli, mitochondria and increase in 'dark' cell frequency were observed (Engelhardt et al. 2001). On the level of barrier, the latter group observed loss of immunoreactivity for Cl-1 and Cl-2, and weaker expression for Cl-11. Analyses of post-mortem brain tissues of MS patients revealed loss of Cl-3 (Kooij et al. 2014). Still, this does not necessarily lead to barrier impairment (Castro Dias et al. 2019).

Very late antigen (VLA-4; integrin α4β1) and melanoma cell adhesion molecule are important for transmigration of T helper (T_H) 1 cell into the CNS in MS *via* endothelial layers. Blockade of melanoma cell adhesion molecule, whose ligand laminin 411 is expressed in the endothelium of the CP, in combination with conditional ablation of α4-integrin on T cells, delayed disease onset (Breuer et al. 2018). One of the most effective MS drug treatments, natalizumab, prevents interaction between T cell VLA-4 ($\alpha_4\beta_1$ integrin = CD49d/CD29, VCAM-1 ligand) and its receptors on brain endothelium and the CP (Ransohoff 2007; Alvarez et al. 2011; Schneider-Hohendorf et al. 2014). Interestingly, there is an upregulation of P-selectin after VLA-4 blockage, indicating that immune cells could use an alternative route for entering the CNS (Schneider-Hohendorf et al. 2014). The drug may downregulate the expression of lipocalin 2, present in the CP stroma, and thus, probably reduce neutrophil infiltration in the CNS (Marques et al. 2012).

Little is known about the involvement of the CP in other autoimmune conditions**. Neuropsychiatric systemic lupus erythematosus** (NPSLE) is an autoimmune disease characterized by neuropathic antibodies infiltration into the CSF, that is believed to occur *via* pathological brain barriers. Gelb et al. (2018) shifted focus on the BCSFB as the primary entry site of the antibodies provoking NPSLE, as they found no changes in integrity if the BBB in the disease, while their findings indicated probable dysfunction of the BCSFB.

Pathogen invasion of the CNS *via* the CP

Penetration *via* the CP to reach the CNS is the substantial mechanism of some viruses, bacteria, fungi, and parasites. Vessel fenestration, absence of glial limitans, and lower epithelial resistance are some of the reasons why pathogens choose the CP as a route of invasion. Three mechanisms used by pathogenic invaders for crossing the BCSFB have been described: transcellular (*via* pinocytosis or receptors), paracellular (*via* disturbed tight and adherents junctions), and '*Trojan horse*' mechanism (pathogens enter tissue *via* infiltrating leukocytes) (Dando et al. 2014; Schwerk et al. 2015). After entering the CP, they infect the tissue and cause an inflammatory response. Some of the pathogens use it also as replication space. Invasion of pathogens into the CP may leave the barrier intact or cause its disruption.

Viruses

The CP serves as an entry and reproduction compartment of **enterovirus**, the viral cause of **encephalitis**, infection with the highest prevalence in children (Feuer et al. 2003; Schneider et al. 2012; Huang and Shih 2015). Usage of *in vitro* BCSFB model derived from human CP papilloma cells, showed that both, apical and basolateral sides of the CPe can be infected by the virus, and during 5-h infection period cells remained viable and barrier showed no disruption (Schneider et al. 2012). Interestingly, the presence of the virus provoked increased chemokine expression (i.e. CXCL1, CXCL2 and CXCL3), but had no significance on T cells migration, as observed *in vivo* (Lucht et al. 1992). Infection with **coxsackievirus B3** (CVB3) was monitored in neonatal mice using recombinant CVB3 expressing the enhanced green fluorescent protein. In early infection stages, the virus was found in high quantities in the CP, also without indications of barrier disruption (Feuer et al. 2003) suggesting virus receptor-TJ binding mechanism of the entrance. In the CPECs of the same animal models was also found **lymphocytic choriomeningitis virus** (Puccini et al. 2014).

The CP is also believed to be the reservoir for **human immunodeficiency virus** (HIV), from where it probably disseminates to other brain areas (Falangola et al. 1995; Petito et al. 1999).

Severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2**), causing the coronavirus disease 2019, primarily infecting respiratory track (Fotuhi et al. 2020), has also been connected with a wide range of neurological complications, like headache, dizziness, stroke, as well as encephalitis/meningitis (Mao et al. 2020; Montalvan et al. 2020; Moriguchi et al. 2020). Still, needs to be determined if the CNS complications arise from systemic inflammation, or from the viral invasion into the CNS. Possible involvement of the CP in any of these viral infecting mechanisms should be taken under serious consideration. Using organoids technology, Pellegrini et al. (2020) showed that SARS-CoV-2 spike protein pseudo- and live-virus cause the CP infection, primarily within the CPe, that expresses the ACE2 receptor. In addition, the same

receptor was not expressed on neurons or neural progenitors, indicating the occurrence of the infection from blood facing side of the tissue. The same group also demonstrated a severe breakdown of the integrity of the BCSFB in presence of viral spike protein.

Bacteria

Haemophilus influenza type B *(Hib),* a known cause of bacterial meningitis in infants and children, whose occurrence has been significantly reduced by routine vaccination (Kim 2010), probably uses the CP as an entry route into the CNS. A study in infant primates, showed in early inflammatory phases the presence of HiB in ventricular spaces, while the CP showed histopathological alterations and immune response, indicating the tissue as an entry route of bacteria (Daum et al. 1978). Pathological changes observed in the CP include **stromal plexitis**, and severe necrosis, as a possible consequence of hydrocephalus, present in the disease (Smith 1987).

The host of Gram-positive agent ***Streptococcus suis*** (*S. suis*) is the pig, causing meningitis, sepsis and endocarditis (Staats et al. 1997). *S. suis* viral agents were histopathologically observed in the CP of these animals (Williams and Blakemore 1990; Madsen et al. 2002). Using inverted BCSFB cell cultivation model, derived from porcine choroid plexus epithelial cells (pCPECs), Wewer et al. (2011) studied transmigration of polymorphonuclear neutrophils (PMNs) through the barrier under inflammatory conditions caused by *S. suis*. Upon stimulation with zoonotic agent, the model showed a high transmigration rate of PMNs, joined with increase expression of adhesion molecules, and alterations in junctional and cytoskeleton organization, although no leukocyte passage through junctions was observed. The fluorescence imaging and electron microscopy revealed that PMNs pass *via* transcellular pathway using funnel-like structures on the apical portion of epithelium, while the transversal route seems to depend on CD11b/CD18 interactions. The CP has been recognized as a potential entry route of *S. suis* also in mice (Domínguez-Punaro et al. 2007). Important to note, the observations were recapitulated in the human HIBCPP model (Schwerk et al. 2012), proving reproducibility of animal model results in humans. The HIBCPP model was also successfully used for the study of bacterial invasion across the CP of **Neisseria meningitidis** (Borkowski et al. 2014), **Listeria monocytogenes** (Gründler et al. 2013) and **Escherichia coli** (*E. coli*) (Rose et al. 2018). Gram-negative bacteria *E. coli*, usually colonizing the intestinal tract, can also cause neonatal meningitis and *E. coli* meningitis (Rose et al. 2018). Neurological symptoms in acute ventriculitis sepsis caused by *E. coli* have been driven into connection with changes in the CP interface (Cardia et al. 1995). Listeria monocytogenes causes choroiditis coupled with meningitis, while at the histological level there is ventricular space necrosis and immune cells extrusion into ventricular spaces (Prats et al. 1992).

There is currently exceeding research about the connection between gut microbiota, and neurological status and mental health (Foster 2013; Hsiao et al. 2013; De Vadder et al. 2014; Kelly et al. 2017). The brain and the BBB have been recognized as communicators within this gut-brain axis (Logsdon et al. 2018). Results showed that gut infection with ***Helicobacter suis*****,** bacteria causes inflammation and disruption of the BCSFB in the mouse brain, while the BBB remained intact (Gorlé et al. 2018).

Fungi

Cryptococcus neoformans (*C. neoformans*) is quite a common CNS fungal infector, as the CSF is free of antycryptococcocal factors, and is usually provoking meningitis (Kumari et al. 2010). To the infection are particularly susceptible immunosuppressed individuals. Studies confirm interaction and passing of fungi though the BBB, and this is by general believe, the route of fungal entrance into the CNS (Chang et al. 2004; Jong et al. 2008; Huang et al. 2012; Tseng et al. 2015). Clinical image of two case reports of the CP plexitis caused by infection with *C. neoformans* in immunosuppressed patients show CP enlargement and enhancement (i.e. may indicate inflammation of the tissue) joined with cystic lesion within basal ganglia indicate also possible involvement of the CP in infection pathology (O'Connor et al. 2020).

Parasites

The CP has been a proven route of the CNS invasion **for trypanosomes**, a causative agent of sleeping disease/sickness (African trypanosomiasis) (Wolburg et al. 2012; Bentivoglio et al. 2018). Analysing electron micrographs of the brain, Falangola and Petito (1993) showed the presence of **Toxoplasma gondii** tachyzoites and pseudocysts in capillaries and stroma of the CP in the majority of AIDS patients deceased during acute necrotizing stages of cerebral toxoplasmosis, and in 20% of the patients with healed lesions, serving as a temporary hostile environment for parasites for further migration between layers of *pia mater*. High frequency of the CP infection with acute cerebral toxoplasmosis identified in the CP (in 53% of all cases tested) was found in the patients with AIDS. Intracranial inoculation with **Mesocestoides corti metacestodes** resulted in parasites within the ventricular area, but infection seems not to alter the BCSFB, but ependyma, that authors suggest as the route of lymphocyte infiltration in the ventricular area in the course of infection (Alvarez and Teale 2007).

Connection of the CP to neurodevelopmental disorders and stress

Neurodevelopmental disorders are a group of etiologically complex diseases, caused by genetic and environmental interactions interfering with proper early brain development, which later in life result in cognitive and behavioural impairments (van Loo and Martens 2007). Several groups have pointed at the presence of alterations in the CP physiology and in composition and flow of the CSF, in this group of conditions (Palha et al. 2012; Arasappa et al. 2013; Marinescu et al. 2013; Kim et al. 2016; Shen 2018; Lizano et al. 2019; Zhou et al. 2020). For example, genetic predisposition, combined with chronic low-grade inflammation caused by stress, perinatal inflammation during pregnancy and sleep disorders, seem to be 'fertile ground' for triggering changes in the CP implicated in onset and progression of autism and schizophrenia, samples of neurodevelopmental disorders (Demeestere et al. 2015). Kim et al. (2016) performed genome-wide expression profiling of the CPs from schizophrenic individuals and found upregulation of genes connected to immune response and inflammation, and their association to disease status, which indicates a potential protective effect of the CP in response to peripheral immune challenges. Neuroimaging pictures of schizophrenic patients show consistent mild lateral ventricular enlargement (Gilmore and Bouldin 2002). One of the consequences of disturbed brain Ca^{2+} homeostasis, probably originating from leakage of the BBB, is calcification of the CP, which seems can serve as a neuroimaging marker of poor-quality evaluation and cognitive impairment of schizophrenic patients (Marinescu et al. 2013). The CP in the perinatal stage responds to the immune status of the mother. The CP of the fetus responds to ongoing inflammation in the mother's body by an accumulation of immune cells within the tissue and intensified production of CCL2 and loosening of the barrier (Cui et al. 2020).

They found a connection between the size of the CP and chronic pain. Namely, the CP in the brain of patients suffering from complex regional pain syndrome (CRPS) showed a 21% volume increase in comparison to age- and gender-match controls, linking the CP with the pathology of the disease (Zhou et al. 2015). Further, the CP might help in 'coping' with stressful situations, as changes in its immunosurveillance seem to participate in stress resilience (Schwartz and Baruch 2012).

Therapeutic potential lying in the CP tissue

The CP shows neurogenic capabilities, and *via* the CSF secretion can stimulate such processes in distal tissues. The tissue itself contains a progenitor neural stem cell population capable of differentiation into various cells of the nervous system (Itokazu et al. 2006; Prasongchean et al. 2015). At the same time it also secretes neurotrophic factors (i.e. glial cell-derived neurotrophic factor, brain-derived neurotrophic factor, and nerve growth factor (Borlongan et al. 2004) that might influence neurogenesis within other CNS areas. These characteristics of the CP hold a very promising regenerative approach in the treatment of CNS injuries. For example, in a case of a stroke, immunohistochemical analysis showed the proliferation inside the CP (Li et al. 2002). Further, grafted syngeneic fragments of CP in the damaged spinal cord of rats resulted in robust regeneration of damaged axons with prolonged effect, while the CPECs grafted into pre-lesioned spinal cord showed differentiation potential towards astrocytes (Ide et al. 2001; Kitada et al. 2001). Transplants of the CPs into the brain of a mouse model of AD (i.e. APP/PS1 mice) showed a reduction of Aβ and p-tau, and memory improvement (Bolos et al. 2014).

Additionally, in close proximity to the CP of the lateral ventricle is the subventricular zone (SVZ), one of the brain areas with active neurogenesis in adulthood (Falcao et al. 2012). The CP acts as a niche of the SVZ, influencing stem cells activities and dynamics (i.e. proliferation and differentiation) *via* the release of secretome that can be modulated in accordance with the physiological state (Falcao et al. 2012; Silva-Vargas et al. 2016).

Usage of encapsulated CPECs cells (Thanos et al. 2010) and the CP implants in animal models showed to be a promising approach in the treatment of Alzheimer's disease, Huntington disease, cancer and stroke (Borlongan et al. 2007; Emerich and Borlongan 2009; Bolos et al. 2014). Encapsulated CPECs were also tested in human subjects suffering from Parkinson's disease, where their usage did not show improvement of the condition (Snow et al. 2019).

Conclusion

Functional CP-CSF interface is of vital importance for the proper functioning of the CNS, as its disturbances have been observed in numerous CNS pathologies. As a connector of the blood circulation and CSF, and an important part of the CNS' immunosurveillance, the CP can sense ongoing peripheral inflammation, provide an adequate immune response, and pass the signal further into other brain areas. At the same time, the studies indicated the presence of the mechanisms for self-protection within the tissue, as well as the ones for prevention of spreading of peripherally originated inflammation through the brain. Comprehensive changes in the CP morphology and functionality play an important part in the onset and progression of physiological aging and neurodegenerative conditions,

such as AD, marked by the presence of toxic protein burden in the brain and oxidative stress. Changes in the CP have been also observed in diseases of autoimmune nature, such as multiple sclerosis, where CP plays a crucial part in the infiltration of devastating immune cells into the CNS, accompanied by the immunological answer of the CP and junctional changes. Anatomical characteristics of the CP make it a 'favourite' route for invasion of many pathogens, even the one's origination from the gut, from where they can further infect the CNS, while some use it as a space for self-replication or reservoir. In the CNS, pathogens can induce profoundly serious conditions, such as encephalitis, meningitis and sepsis. Pathogen infection provokes distinct responses within the CP in terms of inflammation, and barrier disturbance. There are also indications about the CP as an entrance spot of SARS-CoV-2, connected with various neurological complications. Morphological changes in the CP may lead to changes in the CSF dynamics and ICP, as observed in the state of hydrocephalus, which is still being prevalently treated surgically. Tumors can also develop in the CP, mostly in childhood, and an anti-inflammatory treatment approach has been suggested. Disturbances in proper neurodevelopment impacting the CP morphology, and the CSF flow rate and composition, may be the onset of autism and schizophrenia. The CP changes have also been observed in chronic pain, and it is believed that the CP may be helpful in 'dealing' with the stress. Due to neuronal capacities within the tissue, and its support of neurogenic capacities of other CNS sites, it is not a surprise that the CP attracts a lot of attention in regenerative medicine. In this sense, the encapsulated CPECs and CP transplants have shown promising results in animal models of various diseases, while their implication in humans, still desired additional improvements.

In summary, there is much evidence and indications that the CP is an important part of pathological conditions within the CNS, and at the same time tissue that may 'hold the key' for a therapeutic approach to brain regeneration. Said this, future studies of physiological and pathological aspects of the CP, surely represent a significant step forward in the prevention and treatment of various CNS disorders.

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