Choroid plexus trophic factors in the developing and adult brain

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Abstract The choroid plexus (CP), localized in brain ventricles, is the major source of cerebrospinal fluid (CSF) and participates in the blood-CSF barrier. It is essential for brain immunosurveillance and the clearance of toxics, and for brain development and activity. Indeed, the CP secretes a large variety of trophic factors in the CSF that impact the entire brain. These factors are mainly implicated in neurogenesis, but also in the maintenance of brain functions and the vasculature. In this mini-review, we provide an overview of the various trophic factors secreted by the CP in the CSF, and describe their roles in the developing, adult and diseased brain.

Keywords choroid plexus, trophic factors, CSF, neurogenesis, development, adult brain

Introduction

The choroid plexus (CP) is leaf-like structure suspended in the cerebrospinal fluid (CSF) and attached to the ependyma by a thin stalk. It is a highly vascularized structure localized in the lateral, third and fourth ventricles of the brain. CP development and structure are highly conserved between species (Dziegielewska et al., 2001). Its development begins at early stage embryogenesis after neural tube closure, when the hindbrain CP in the 4th ventricle first appears, followed by the telencephalic CP in the lateral ventricles and the diencephalic CP in the 3rd ventricles. Two cells types are implicated in the formation of CPs: neuroectoderm cells for the CP epithelium formation; and the mesoderm for the formation of the CP stroma (Strazielle et al., 2005; Liddelow, 2015; Lun et al., 2015). The developing CP might also contain neural progenitor-like cells as precursors of neurons observed later in CP. These cells could assist CP formation during embryogenesis by providing a neural regulatory network that modulates CP functions (Itokazu et al., 2006; Huang et al., 2011; Prasongchean et al., 2015). The development, formation and specification of CPs is guided

by specific growth and transcription factors (Johansson, 2014; Liddelow, 2015).

The CP is the principal source of CSF in the brain (Spector et al., 2015a) and is responsible for the maintenance of brain homeostasis through regulation of fluid and electrolyte balance in the central nervous system (CNS). The composition of CSF is very similar to plasma and is secreted via an active mechanism by choroidal cells. CP maintains CSF composition by filtration and by controlling solute and water movements across the epithelium (Damkier et al., 2013). The CP is also part of the brain barrier that forms a blood-CSF barrier implicated in CNS immunosurveillance (Engelhardt et al., 2001; Meeker et al., 2012; Kunis et al., 2013). It eliminates toxic peptides from the brain via various transporters: CP is a sort of “kidney” in the brain (Spector and Johanson, 2010; Saunders et al., 2013; Spector et al., 2015b). Also, many functions are attributed to the CSF, such as the regulation of intracranial pressure and brain volume, nutrient transport, drainage, immune regulation, and the transport of proteins and peptides coming from the CP (Chodobski and Szmydynger-Chodobska, 2001; Redzic and Segal, 2004; Strazielle et al., 2005; Spector et al., 2015b). Indeed, the CP secretes many proteins and peptides in the CSF, such as hormones, growth factors, homeoproteins, etc, which can easily diffuse throughout the brain (Johanson et al., 2011b) and affect both developing and adult brain. In this short review, we will focus on growth factors and

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neurotrophic factors expressed by the CP and explore their implications in the developing and adult brain, in health and disease.

Impact of choroid plexus trophic factors in the developing brain

During early brain development, the ventricles occupy the majority of the cranial volume and are filled with circulating CSF that originates from choroid epithelial cells. This fluid contains many proteins that regulate brain development and neurogenesis by signaling and feeding rapidly dividing progenitors along the ventricular walls (Zappaterra and Lehtinen, 2012; Falcão et al., 2012; Gato et al., 2014). Upon secretion into the ventricle, molecules from the CP are conveyed by CSF bulk flow to the various regions of the developing brain (Miyani et al., 2003). Also, certain proteins secreted by CP cells impact the development and maintenance of the CP itself via autocrine signaling. Among these proteins that orchestrate proper brain development are numerous growth factors, neurotrophic factors and morphogens (Fig. 1).

The major growth factors found in embryonic CSF include transforming growth factor (TGF), insulin growth factor (IGF) and fibroblast growth factor (FGF). The TGF- β family, including bone morphogenic proteins (BMPs) and the growth differentiation factors (GDFs), are involved in the developing brain by promoting cell growth and proliferation, and inhibiting neuronal death (Falk et al., 2008). BMP7 has recently been shown to regulate the survival, proliferation and neurogenic properties of neural precursor cells during brain corticogenesis (Segklia et al., 2012). BMP7 from CP also directly attenuates the differentiation of the adjacent neural progenitors, maintaining a pool of progenitors (Krizhanovsky and Ben-Arie, 2006). TGF- β 2 and TGF- β 3 are important regulators of neuron survival, while GDF-15 is important for developing and injured neurons, via its protective action against death (Strelau et al., 2000). BMPs are also important for the specification of CP epithelium. The inhibition of BMP signaling can result the absence of CP (Hébert et al., 2002), whereas BMP4 alone is sufficient to induce CP epithelial cells from embryonic stem cell-derived neuroepithelial progenitors (Watanabe et al., 2012).

IGF acts on the developing CP for its function and maintenance (Nilsson et al., 1996) and is expressed and secreted by CP cells (Salehi et al., 2009; Lehtinen et al., 2011). During development, IGF promotes the proliferation, migration and differentiation of immature glial and neuronal cells (Lehtinen et al., 2011; Ziegler et al., 2012).

In early CP development, FGF expression, particularly FGF2, modulates gene expression and activity, suggesting that FGF signaling maintains CP integrity and function (Greenwood et al., 2008). Secreted FGF2 has also been

shown to have a role in the developing brain by regulating cell proliferation/neurogenesis and corticogenesis (Vaccarino et al., 1999; Mashayekhi et al., 2011).

Neurotrophic factors are also highly expressed in the developing brain, during the phase of neurogenesis (Maison-pierre et al., 1990). Nerve growth factor (NGF) and neurotrophins (NT) are all expressed and secreted by the CP in the CSF. NGF, NT3 and NT4 promote proliferation, survival, and neurochemical differentiation of selected neuronal populations in the CNS (Xia et al., 2000; Das et al., 2001; Mashayekhi et al., 2009).

The CP secretes other proteins and molecules that impact brain patterning and activity. Sonic hedgehog (Shh) contributes to the CP development by acting on the progenitor pool of CP epithelial cells, and permitting CP expansion (Huang et al., 2009). Shh has also been shown to coordinate the vascular development in CP (Nielsen and Dymecki, 2010). Transthyretin (TTR), also known as prealbumin, is secreted by the CP and carries the thyroid hormone thyroxine and retinol binding protein. TTR and thyroid hormones have an important role in regulating brain expansion and growth (Alshehri et al., 2015). Some studies have shown that CP expresses γ -aminobutyric acid (GABA) and glutamic acid decarboxylase 65 (GAD65), suggesting a production of non-neuronal GABA which can modulate the properties of neural progenitors in the developing cortex (Tochitani and Kondo, 2013).

Impact of choroid plexus trophic factors in the adult brain

In the adult brain, while the ventricles now occupy very little volume, the CP continues to secrete growth and transcription factors in the CSF, including FGF, epithelial growth factor (EGF), TGF- β , platelet derived growth factor (PDGF), IGF, vascular endothelial growth factor (VEGF), and the homeoprotein Otx2 (Fig. 1). Many of these factors are implicated in either adult neurogenesis, plasticity, cognition or angiogenesis (Marques et al., 2011; Falcão et al., 2012; Stolp and Molnár, 2015). Indeed, the CSF can impact the entire brain, due to its capacity to diffuse around the brain and in the parenchyma, along vessels (Iliff et al., 2012; Brinker et al., 2014).

FGF2 injected or infused in the CSF has been shown to increase adult neurogenesis in the subventricular zone (SVZ) and the dentate gyrus (Wagner et al., 1999; Cheng et al., 2002). FGF2 and EGF also maintain neural niche architecture and cell lineage progression (Jin et al., 2003). EGF, infused in the ventricle, increases the proliferation of progenitors cells in the SVZ, and induces their migration and differentiation (Craig et al., 1996; Doetsch et al., 2002).

PDGF is implicated in the maintenance of adult cell types. There is evidence that PDGF contributes to the differentiation

Figure 1 Secretion and roles of trophic factors in the developing and adult brain. The choroid plexus (CP) secretes many trophic factors that impact the developing and adult brain, in health and in disease. During development (top panel), trophic factors guide brain formation through their roles in neurogenesis, vasculature development and brain expansion/maturation. In the adult brain (middle panel), the CP continues to secrete trophic factors that impact and maintain adult neurogenesis and brain maturation/function. In some diseases (bottom panel), such as those involving neurodegeneration, the CP atrophies and/or trophic factor secretion is altered. These changes can lead to neuroinflammation, impaired neurogenesis, and compromised vasculature that ultimately result in brain deficits. CP: choroid plexus, CSF: cerebrospinal fluid, VEGF: vascular endothelial growth factor, IGF: insulin growth factor, FGF: fibroblast growth factor, EGF: epithelial growth factor, PDGF: platelet-derived growth factor, NT: neurotrophins, TGF: transforming growth factor, TNF: tumor necrosis factor, IFN: interferons, NSC: neural stem cells.

of oligodendrocytes in adulthood, and increases proliferation in SVZ (Jackson et al., 2006). SVZ progenitors express PDGF receptors and increase proliferation in response to PDGF signaling (Moore et al., 2014).

In adult brain, VEGF directly regulates the proliferation of adult stem cells, and promotes cell survival and axonal outgrowth (Schänzer et al., 2004; Mackenzie and Ruhrberg, 2012). VEGF is also implicated in the maintenance of CP in adult brain by sustaining normal vasculature (Maharaj et al., 2008). It also affects the proliferation, growth and migration of cells by helping to form angiogenic niches important for neurogenesis, and by acting directly on cells to promote proliferation (Jin et al., 2002; Ruiz de Almodovar et al., 2010; Licht et al., 2010; Mackenzie and Ruhrberg, 2012).

IGF-II promotes the self-renewal of neural progenitors/stem cells (Ziegler et al., 2012, 2015), and the IGF family has been shown to stimulate neurogenesis and protect cells against injury (Ziegler et al., 2015). IGF also enhances memory by its neurotrophic action on glutamatergic synapses, within hippocampal circuits (Werner and LeRoith, 2014). However, Igf2 levels are greatly reduced in the adult compared to embryonic CSF (Lehtinen et al., 2011). This same study also showed that several BMPs continue to be expressed in adult CP and retain similar CSF activity (Lehtinen et al., 2011).

Neurotrophic factors have a reduced role in adult CSF. Brain-derived neurotrophic factor (BDNF) can increase adult proliferation and cell survival (Pencea et al., 2001; Binder and Scharfman, 2004), while NT3 is implicated in the quiescence and long-term maintenance of adult stem cells (Delgado et al., 2014). BDNF also appears essential for molecular mechanisms of synaptic plasticity (Binder and Scharfman, 2004; Budni et al., 2015).

Others molecules secreted by the CP in adulthood that are implicated in cell proliferation, self-renewal, survival, and migration include Wnt, Shh, ephrins, semaphorins, Slits, and Robo (Falcão et al., 2012). Transcription factors have also been found in CSF. The Otx2 homeoprotein is secreted by CP in postnatal CSF and accumulates in cortical interneurons to help regulate the timing of periods of heightened circuit plasticity shaped by sensory experience (Spatazza et al., 2013).

Impact of choroid plexus trophic factors in aging and diseases

Aging impacts CP: the secretion of CSF is reduced and the production of growth factors decreases (Fig. 1) (Redzic et al., 2005; Chen et al., 2012). CP cells themselves are impacted, with morphological and metabolism modifications, and decreased capacity of neuroprotection. Brain permeability can increase with age, due to attenuated CP barrier, potentially resulting in the entry of inflammatory and toxic molecules in the brain. CSF turnover is modified, resulting in

reduced ability to clear proteins from CSF, which can lead to an accumulation of toxic molecules in the aged brain (Preston, 2001; Emerich et al., 2005).

Furthermore, aging is accompanied by reduced production of growth factors, leading to a decrease in adult neurogenesis (Emerich et al., 2004). However, treatment with growth factors during aging could partially revitalize neurogenesis: as CP cells produce a huge quantity of IGF, which is important for neurogenesis and cell turnover, aging CP could have significant consequence for tissue repair and brain functioning. IGF-1 supplementation can reverse cognitive deficits induced by aging, and can restore normal hippocampal activities (Ashpole et al., 2015). Growth Hormone (GH) has been shown to have the same effect on aging brain (Ashpole et al., 2015). With age, the production of BDNF, NGF and GDNF is modified, resulting in reduced neuronal survival and neurogenesis eventually leading to cognitive impairment (Budni et al., 2015). On the other hand, CP produces new molecules during aging, such as interferon type I (IFN-I), whereas IFN-II production decreases. Changes in IFN levels lead to modified brain function, such as cognitive deficits, hippocampal dysfunctions, neuroinflammation, and decreased neurogenesis (Baruch et al., 2014).

Aging is strongly associated with Alzheimer's disease (AD), the most common neurodegenerative disease. AD is characterized by cognitive deficits, memory loss and neuronal loss, and is linked to modifications in CP functions. In AD, CP can have an altered structure (Serot et al., 1997, 2001). It normally has a role in the clearance of amyloid fragments, a hallmark of AD, but with disease progression, this CP function is altered and the clearance becomes incomplete (González-Marrero et al., 2015). The barrier and "kidney" functions of CP appear to be less efficient. This dysfunction is associated with a reduction in trophic factor production, leading to reduced neuroprotection against AD hallmarks (Krzyzanowska and Carro, 2012). Certain trophic factors can help the clearance of toxic peptides, such as FGF2 and IGF-1 (Johanson et al., 2004; Carro et al., 2006). But with the progression of AD, a vicious circle appears: low levels of trophic factors induce clearance deficits, which leads to a decrease in factor secretion by the CP. The production of BDNF, NGF and GDF is also modified in compensation during AD: in early stages their concentrations increase, whereas in later stages, they are decreased. In later stages, these modifications probably encourage neuronal loss and memory deficits (Budni et al., 2015; Forlenza et al., 2015). Neuroinflammation is present throughout all AD stages. In early stages, IFN-I, IFN-II and TNF- α levels contribute to neuroprotection by increasing the migration of new cells in the brain (Ben-Hur et al., 2003). But in later stages, IFN-I and IFN-II CSF levels are increased, leading to cell death, suggesting a role in the development of AD pathology (Mesquita et al., 2015).

In other neurodegenerative diseases, CSF trophic factors are also modified. In amyotrophic lateral sclerosis (ALS),

FGF is increased in the CSF and serum of patients, possibly as a compensation phenomenon for protection against cell apoptosis and neuronal loss (Gong et al., 2015). In AD, ALS and Huntington's disease (HD), modified VEGF levels lead to vascular and neuroprotection impairments (Storkebaum and Carmeliet, 2004). In ALS, it has been shown that altered VEGF levels are indicative of the activation of compensatory responses, which may reflect the disease progression (Gao et al., 2014).

Neuroinflammation is often associated with neurodegenerative diseases. Accordingly, many inflammatory factors, which could also act as neurotrophic factors, are expressed. Increases in IFN-I, IFN-II and TNF- α levels are also changed: they are linked to neurodegeneration pathways in Parkinson's disease (PD), ALS, multiple sclerosis (MS), while contributing to neuroinflammation (McCoy and Tansey, 2008). Other cytokines and pro-inflammatory proteins are also released by the CP, such as CXCL12 and IL1- β , and have been shown to decrease adult neurogenesis as a consequence of brain inflammation (Stolp and Molnár, 2015).

The secretion of trophic factors can also be regulated during brain injury, such as stroke. During such an event, CP is altered and the barrier can become compromised. However, CP can react to protect the brain against the lesion/ischemia and to induce brain regeneration/repair. CP expression of trophic factors, such as IGF-II, EGF, NGF, GDNF, BDNF, VEGF, and TNF, are implicated in the stimulation of adult neurogenesis, angiogenesis and neuroprotection/cell survival (Johanson et al., 2011a; Zappaterra and Lehtinen, 2012). CP cells have also been implicated directly in tissue regeneration, acting as progenitor cells in injured brain (Li et al., 2002).

Under stress conditions, trophic factor levels are modified in the CSF, owing to altered CP secretion and structure, and might be linked to psychiatric disorders. In major depressive disorder (MDD), modified expression of FGF family factors alter hippocampal functions pertaining to mood and emotions (Aurbach et al., 2015). However, another recent study found no difference in CP growth factor production in MDD patients (Turner et al., 2014), other than a decrease in TGF- β . It has also been shown that stress can modify BDNF, IGF1, TNF- α and IL1- β production/expression in CP (Sathyanesan et al., 2012). In bipolar disorder (BD), BDNF is decreased, with implications in the depression or "active" phases, possibly linked to its role in synaptic function and memory consolidation (Pillai et al., 2010; Rabie et al., 2014). The levels of NGF, BDNF, NT4 and NT5, GDNF, IGF1 and VEGF can be modified during different disease stages and with varying outcomes for BD pathology (Scola and Andreazza, 2015).

Outlook

The CP secretes many different trophic factors, important in the developing and adult brain. These factors act in the

normal brain, but they are also implicated and modified in many diseases. The potential therapeutic effect of CP cells has not escaped attention, and their transplantation in the diseased brain has been envisioned. The CP is itself a potentially powerful therapeutic target, as it provides a means of suppressing or activating trophic factor levels throughout the brain.

Compliance with ethics guidelines

K. Arnaud and A. A. Di Nardo declare they have no conflict of interest. This article does not contain studies with human or animal subjects performed by the authors.

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