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The ChP-CSF System; Dynamic Regulator of Brain Homeostasis and Adult Neurogenesis

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Abstract

One of the most understudied tissues of brain, choroid plexus (ChP), universally recognized as the source of cerebrospinal fluid (CSF). ChP and its secretions, CSF have significant intimacy with health status of brain and they dynamically regulate the central nervous system (CNS) related diseases. In spite of various experimental issues and lack of clinical salience, resent research sparked some new hypothesis, which provides the possible means how ChP and CSF regulate nervous system structure and function. As the key producer of cerebrospinal fluid, the choroid plexus endows with an essential and unique protective system, brain development, homeostasis and disease conditions that are merrily regulated by active signaling milieu of CSF. From the childhood to adult, the role of CSF and the key neurogenic pathways have been illustrated by various scientific research groups. CSF is an excellent source of biological information of central nervous system and the identification of putative CNS disease biomarkers highlighted recently. The families of proteins which are involved in development, neuronal cell growth, maturation, migration, neurotransmitter mediated cellular communication represent the CNS pathogenesis and help in clinical management of CNS diseases. The advanced proteomic researches have enabled to improve the characterization of CSF in diseased brain. CSF function continued to be an intensive area of research today. As the ChP-CSF system interacts with essentially every other system in the CNS, in this review article, the igniting role of CP-CSF function will be discussed.

Keywords: Choroid plexus; Cerebrospinal fluid; Neural stem cells; Neurogenesis.

Introduction

The first and foremost investigation of the cerebrospinal fluid dates back to 1700 BC and the thoughts of Hippocrates (460–375 BC), hydrocephalous which he described that too much "water in head". Consequently in 300–250 BC Herophilus described the name "Chorioidmennix" which is now known as choroid plexus. In nineteenth century, Harvet Cushing made the pivotal discovery that the choroid plexus (ChP) is a highly vascularized tissue loaded in each ventricle of the brain and it secretes Cerebrospinal fluid (CSF).[1] CSF represents an independent circulatory system for the brain and spinal cord. Today we know that the CSF is produced primarily by the choroid plexus, located in each ventricle in the brain and full range function of CSF is under investigation to unfold the role of CSF in regulating various physiological function of the body. The continuous

exchange of CSF in brain serves as a "sink" that flushes the ventricular system of debris and unused injury products. The disruption of ChP-CSF homeostasis happens during brain injury.[2] ChP-CSF is an understudied area as it is being observed that in an international meeting like Society of Neuroscience, in the year 2014, out of 17,000 (seventeen thousand) of abstracts of brain related topics only 9 (nine) abstracts/studies were from choroid plexus.[3] Damage to choroid plexus, alterations in CSF secretions, increased leucocytes within brain and CSF, decreased clearance of toxins, catabolites, proteins leads to diminish supply of nutrients and growth factors to the brain. Also it is believed that gradual repair of CP-SCF system, returning back to homeostasis, correlates with the recovery from brain injury and promote neuroregeneration and neuroprotection. In vertebrate brain, choroid plexus is the important secretory tissue which is a highly vascularized secretory epithelium responsible for producing CSF. The diverse and active roles of the CSF in developing brain as well as in adult brain are unfolding recently. The missing links between the chronic neurodegenerative disorders and the interlink between CSF and immune network are yet in an exploring stage. In CNS, in contrast to blood brain barrier (BBB) which is composed of endothelial tight junctions, choroid plexus (ChP), the blood-CSF barrier is the unique barrier in brain which composed of epithelial tight junction with fenestrated endothelium and acts as educative gate to access selective cells into the brain, depending upon the need. ChP is the only epithelial interface of brain, through which CNS parenchyma deliver the signal indicating the need and the circulation provide signal recruiting help. Hence, through the circulating immune milieu of the CSF, ChP dysfunction can be modulated in well advance to protect the CNS from neurodegeneration. The regulatory T-cells present at CP controls the local as well as remote health of brain.[4] Studies from experimental animal model suggest that in healthy brain, immune cells are excluded out from the brain[5], which strongly emphasizes that tight regulation of immune cells directed by signaling molecules from CNS. In neurodegenerative conditions, either effecter T-cells declines or suppressor T-regulatory cells elevated in circulation.[6]

Physiology of ChP-CSF

The intraventricular organ choroid plexus is a highly vascularized secretory epithelium.[7] The essential cells of choroid plexus contain tight junctions that function and prevent passive diffusion of molecules from choroid vasculatures and interstitial space into the CSF. In other words, choroid plexus actively secretes CSF into the ventricles and creates the blood-CSF barrier. CSF is the clear fluid that cushions and delivers nutrients to the central nervous system (CNS). In every 24 hours CSF is renewed about four times and the mean CSF value is 150 ml, out of which 25 ml is in the ventricle and 125 ml in the subarachnoid spaces. Choroid plexus takes the predominant role to secrete CSF, however brain interstitial fluids, ependymal capillaries may also play a poorly defined role in CSF secretion. CSF plays important role in providing hydro-mechanical protection to the CNS and also have significant contribution for brain development.[8] and regulation of interstitial fluid homeostasis, which influence neuronal functioning. In addition to homeostasis of the interstitial fluid of brain parenchyma and regulation of neuronal functioning also ruled by CSF. The physiological CSF pressure values vary according to individuals (10–15 mm Hg in adult and 3–4 mm Hg in infants). The mechanism of CSF pressure has not been fully elucidated and many current literature states CSF pressure variation occurs like various factors such as systolic pressure, respiratory cycle, abdominal pressure, and jugular venous pressure, state of arousals, physical activity and posture.

CSF in Developing Brain

Although study of CSF dates back to early Egyptians and Greek, just before 100 years ago, Harvey Cushing observed that ChP secretes CSF into the brain ventricle.[9] Approximately at 44 days of post-ovulation, in human embryo, the choroid plexus begins to develop in the fourth and lateral ventricle and become quite large by 9-week gestation. By this time, ChP fills a large part of the lateral ventricle and spanning the length of the fourth ventricle. An adult human produces approximately 500 ml of CSF daily from which 150 ml circulates throughout the CNS and CSF turnover about three to four times per day.[10] The content of CSF is 99% water, primarily produced by Aquaporin channels located on the apical membrane of epithelial cells. CSF is a rich source of protein, lipids, ions, hormones, glucose, cholesterol and many other molecules and metabolites. Biological function of CSF and its resident factors have been speculated to influence wide range of behavior including sleep, appetite and circardian rhythm and locomotion activity.[11] Melatonin present in CSF acts as a free radical scavenger and antioxidant and is believed that it is one of the neuroprotective agents.[12] The expression

of transthyretin[13] indicates the differentiation of choroid plexus. A number of growth factors and transcription factors regulate the localized formation of ChP. The expression of high level of BMP (bone morphogenetic protein) signaling and expression of growth factors like Wnt1, GdF7 and transcription factors in the hindbrain. ChP develops from the lower limbic lip. Sonic hedgehog (Shh) promotes proliferation of fourth ventricle ChP progenitor cells, as well as the choroid plexus mesenchyme.The powerful trophic factors present in CSF are essential requisites during early development. Rapid expansion of the early developing brain occurs due to the pressure created by osmotic gradients of accumulated CSF.[14]

ChP Secretome Changes with Advanced Age

Cerebrospinal fluid secreted by the ChP contain majority of proteins (80% approximately) are blood derived and remainder consists of brain derived. Recent advances in mass spectrometry techniques, helps in better understanding the CSF proteome. The composite nature of CSF proteome profile consists of hundreds of proteins of the extracellular matrix, regulators of osmotic pressure, ion carriers, hormone binding proteins, regulators of lipid metabolism. Various enzymes and their regulators.[15,16] The role of CSF during brain development has been studied across the species including zebrafish, chicken rodents, marsupials and other many other animals. All the studies have demonstrated that CSF share many similar compounds among all. The growth factor signaling and the ventricular enrichment of phosphotyrosine and phosphor-ERK activates the neural precursor cells and promotes neural stem cells and cortical neurons. Starting from embryonic brain development, CSF factors (growth factors) such as FGFs (fibroblast growth factors), IGFs (insulin like growth factors), Shh (sonic hedgehog), RA (retinoic acid), BMP (brain morphogenic protein), Wnt and other responsible factors for proliferation, differentiation and maturation of brain cells, each processes regulated by CSF.[17]

CSF Regulates Neurogenesis

An active signaling milieu, CSF has attracted renewed interest for its improved characterization in neural stem cell signaling (neurogenic signaling). In the developing and adult brain, due to its immediate close contact with neural stem cells CSF system opens an avenue for novel and exiting therapeutic approach. Many current literatures come up with similar view saying how CSF regulates mammalian brain development. The interventricular organ, choroid plexus is a highly vascularized secretory epithelium.[18] The epithelium cells of choroid plexus contain tight junctions that function and prevent the passive diffusion of molecules from choroid vasculature and interstitial space plexus actively secreted CSF into the ventricles and create blood–CSF barrier. At lateral ventricle, ChP is the primary souce of CSF, where subventricular zone stem cell niche is largely ignored. Proliferation and activation of subventricular zone stem cells rely on the secretory factors and supporting function of lateral ventricular choroid plexus (LVCP). This compartment act as a key regulatory compartment for stem cell niche and has functional effect throughout the lifespan. Stem cell resides in specialized niche and undergo dynamic changes throughout life span, in response to extrinsic changes, physiological stages of aging etc. CSF provides the homeostatic support for the brain and the complex milieu of CSF which contain active signaling cues from local and long range sources. During brain development as well as in adult, CSF plays an important role in providing migratory role of neural stem cells. The physiological signals from circulatory system and nervous system and immunesystem get integrated dynamically and act as a sensor for coordinated response.

CSF as Biomarker for Neurological Disease

Biomarkers are the molecules that act as an indicator of biological and physiological process as well as pathophysiological progress or pharmacological responses to therapeutic interventions. Sometimes the commonly used word "surrogate markers" is used for biomarkers. For neurological status, CSF is used as best biomarker and it reflects the single clinical or pathological aspects of chronic neurodegenerative disease. Numerous CSF-Biomarkers are predicted and there are some common CSF biomarker. There is a huge demand for biological markers at early stages of disease, which can identify the prognostic value for patients and benefits them for specific treatments. Many neurological diseases originated with different pathological conditions follow similar final pathway during neurodegenerations. Hence in a real clinical practice, in addition to several diagnostic criteria, biomarkers present in CSF provide an essential criterion for the better way of therapeutic attributes. Accumulation of neurofilament, the measure cytoskeletal protein of neuron, is a distinct feature of in several neurological diseases. The increased

lead of CSF neurofilament NF-L correlates with ongoing neurodegeneration in brain. The NF-L is a potential translational dynamic biomarker of neurodegeneration. Total tau (T-tau) and GFAP (glial fibrillary acidic protein) is the marker for glial damage. Other promising source of biomarkers are phosphorelated tau, neuron specific enolase, N-acetyl aspartic acid, 13-3-3 proteins.[19] As related changes in neuronal health status reflect in CSF, central nervous system diseases are clinically heterogeneous and these diseases share a chronic progressive degenerative phenomenon. So CSF holds the important challenges to diagnostic and therapeutic progress in neurological health. Starting from brain and spine, cerebrospinal fluid (CSF) analysis is a way of looking for conditions that affect whole central nervous system as a result of which series of laboratory tests provides an amount of information on sample of CSF.

CP-CSF System for Therapy

Despite the several advances in the therapeutic approaches and medicine, effective therapies have not been achieved for CNS diseases due to multifunctional reason. The complexity of the CNS is itself an additional difficulty. The direct injections into the CSF via intrathecal or intraventricular may achieve certain clinical success.[20] However the downsides are many as that need to be done repeatedly over a lifetime and patient safety is a measure concern. At this point of time "cell based therapy" brings a hope for treating many CNS diseases as they are long-lived, safe and provide long-term delivery to the CSF, which can circumvent the issues and provide stratagies for CNS disease treatment. The ChP based cell therapies brings promise to show improvement in therapy by transplantation of primary choroid plexus; i.e. encapsulated porcine.[21] Major function of CSF is secretion, transport, detoxification and barrier function. Throughout life, the health of the nervous system actively depends upon the Chp-CSF system and the coordination of ChP-CSF system is essential from embryonic to the adult. A new era for studies of ChP-CSF system has began and understanding the constituency of the CSF action will not only guide the basic biology and stem cell research, but also propel the current and potential uses in pharmacologic sand surgical therapies for neurodegenerative disease, cancer and hydrocephalus and beyond. In the field of ChP-CSF system, the sparking initiative researches will harness the Chp-CSF system and will offer the great service for nervous system repair and diminish the neurodegenerative disease. CP-CSF system plays crucial role in development and maintenance of the CNS and is accepted as fluid cushion and sink for nervous system waste in vertebrates. The active role of this dynamic system have unfolded in various recent studies and focused to study, how CP-CSF regulate the overall health of nervous system may bring new paradigm shift in treatment of neurological diseases. Extrinsic and intrinsic molecular mechanism that guide the specification of ChP cells and their proliferation into a highly structured organ.

Despite the immense potential of CP-CSF system to regulate the CNS, it remains one of the must understudies is of neurobiology. Potential of ChP targeted therapies in rejuvenating and repairing of the CNS. The information of this review would help to promote the further investigation and to study intimately to understand the tremendous capacity of CP-CSF system and to harness the potential to repair the aged and diseased brain. The functional plasticity of healthy brain, neurogenesis and hippocampal dependent cognitive abilities are intimately involved with immune cells and neurotrophic factors.[22,23] As long as the activity of monocyte derived macrophage is regulated, their recruitment is well controlled. In maintenance of brain plasticity in health, neurodevelopmental and other neurological diseases, role of immune cells are well appreciated.[24,25] Moreover, sever inflammation impairs neurogenesis, which address that regulated activity of immune cells required for homeostasis of healthy brain and maintenance of brain plasticity.[26]

So the potential role of immune cells in CSF of natural health and plasticity urging the need for open the door of our clear understanding.

Abbreviations

BBB: Blood brain barrier
BCSFB: Blood CSF barrier
ChP: Choroid-plexus
CNS: Central nervous system
CSF: Cerebrospinal fluid
NSC: Neural stem cells

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