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Review Article

Meninges: from protective membrane to stem cell niche

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Abstract: Meninges are a three tissue membrane primarily known as coverings of the brain. More in depth studies on meningeal function and ultrastructure have recently changed the view of meninges as a merely protective membrane. Accurate evaluation of the anatomical distribution in the CNS reveals that meninges largely penetrate inside the neural tissue. Meninges enter the CNS by projecting between structures, in the stroma of choroid plexus and form the perivascular space (Virchow-Robin) of every parenchymal vessel. Thus, meninges may modulate most of the physiological and pathological events of the CNS throughout the life. Meninges are present since the very early embryonic stages of cortical development and appear to be necessary for normal corticogenesis and brain structures formation. In adulthood meninges contribute to neural tissue homeostasis by secreting several trophic factors including FGF2 and SDF-1. Recently, for the first time, we have identified the presence of a stem cell population with neural differentiation potential in meninges. In addition, we and other groups have further described the presence in meninges of injury responsive neural precursors. In this review we will give a comprehensive view of meninges and their multiple roles in the context of a functional network with the neural tissue. We will highlight the current literature on the developmental feature of meninges and their role in cortical development. Moreover, we will elucidate the anatomical distribution of the meninges and their trophic properties in adult CNS. Finally, we will emphasize recent evidences suggesting the potential role of meninges as stem cell niche harbouring endogenous precursors that can be activated by injury and are able to contribute to CNS parenchymal reaction.

Keywords: Meninges, leptomeninges, arachnoid mater, pia mater, corticogenesis, neurogenesis, neural stem cells, neural progenitors, stem cell niche

Introduction

Meninges are formed by three tissue membranes that are primarily known as wrappers of the brain. They consist of dura mater, arachnoid and pia mater. The dura mater or pachymeninx (*pachy*-thick) is the outer membrane and forms a sac that envelops the other meningeal layers. It surrounds and supports the dural venous sinuses and it reflects in three infoldings, the first separating the two hemispheres of the cortex (falx cerebri), the second between the cerebellum and the occipital lobe (tentorium cerebelli and falx cerebelli) and the third covering the pituitary gland and the sella turcica [1]. The leptomeninges (*lepto*-, thin) are the inner membranes formed by two layers: the outer is named arachnoid (*arachn*-, spider) and the inner pia mater (*pia*-, tender) [1]. The arachnoid is linked to the pia by arachnoid trabeculae that span the subarachnoid space filled with cerebrospinal fluid (CSF) produced by choroid plexi [1].

The first known anatomical descriptions of the meninges and of the cerebrospinal fluid have been found in the Edwin Smith Papyrus, an Ancient Egyptian medical text on surgical trauma (ca. 1600 BCE). The text seems to be related to previous manuscripts attributed to Imhotep, an Egyptian physician (ca. 3000-2500 BCE) [2].

The primary function commonly attributed to meninges and CSF is to protect the central nervous system (CNS). This is mainly because meninges provide a tight anchoring of the CNS to the surrounding bones able to prevent side-to-side movement and providing stability. In the head, the external part of the dura, the periosteal layer, is tightly fixed to the skull. In the spinal cord, in addition to the periosteal layer, 21 pairs of denticulate ligaments pass from pia through arachnoid attaching to dura mater and

vertebral bones. Moreover, meninges are filled up with the CSF letting the CNS "float" in it and thus cushioning hurting events [1].

In this review we will give a comprehensive view of meninges in the context of a functional network with the neural tissue. We will revise the literature highlighting the development of meninges, their distribution in adult CNS, their role in cortical development and in CNS homeostasis. Moreover, we will analyse new data suggesting the potential role of meninges as a stem cell niche harbouring endogenous injury-activated neural precursors.

Meninges development and distribution

In the early embryo, the neural tube is enveloped by a layer of mesenchymal cells that will result in the primary meninx. Both mesenchymal and neural crest-derived cells appear to be involved in the formation of the primary meninx that will differentiate during the embryo development by forming two different layers: the dura mater and the leptomeninges respectively [3]. Embryologic and anatomic differences appear to exist between the meninges of the brain and the spinal cord. Encephalic meninges have been described to originate from both the mesenchyme and the encephalic neural crest, while the meninges of the spine and of the caudal regions of the head originate from the paraxial mesenchyme [4, 5]. The three meningeal layers are formed starting from a single pial meshwork structure composed of cells that progressively generates next to the pia mater two other arachnoid layers: an inner layer of cells with round nuclei and an outer layer of cells with oval nuclei; at the same time the dura mater layer forming next to the arachnoid shows spindle shaped cells with collagen deposition [6]. Similar developmental morphogenesis is observed in rat and human embryos [5, 7].

In adult CNS the meninges cover and penetrate the brain deeply at every level of its organization: as large projections between major brain structures, as sheaths of blood vessels and as stroma of the choroid plexus [1]. Meninges also project between substructures. A major meningeal projection is located underneath the hippocampal formation [8, 9]. This meningeal projection is continuous with the choroid plexus stroma. The cranial pia mater actually envelops the cerebrum and cerebellum and extends into the sulci and fissures. It also forms the non-neural roof of the third ventricle, the lateral ventricle and the fourth ventricle [10]. The reconsideration of the distribution of meninges in the CNS (**Figure 1**) set the stage for a more complex consideration of meningeal functions as modulator of CNS in homeostasis and disease.

Meninges and the brain vasculature

The primitive meninx is also the site of origin of a complex vascular plexus that evolves to give rise to the brain vasculature [11-15]. The extracerebral vascular (pial) meningeal compartment is the first to develop by forming the major venous sinuses, the arachnoidal arteries and the veins that cover the surface of the developing and adult cerebral cortex [15]. Subsequently, sprouting vascular elements from pial capillaries pierce the brain external glial limiting membrane and penetrate the cortex establishing the intracerebral microvascular compartment. Every perforating vessel is associated to extroflexions of the meninges; a perivascular space is thus formed limited by the basal laminae of the vasculature on the inner side and of the glia on the external side. The pial vascular plexus vessels play an essential role in the brain intracerebral microvascularization and retain, throughout life, a remarkable activity, with continuous remodeling and readaptation to local functional needs [15].

The anatomical basis for the extension of the subarachnoid space within the perivascular spaces has been established in several mammalian species, including man [16-21, 22]. It has been shown that the pia mater on the surface of the brain and spinal cord reflects onto the surface of blood vessels in the subarachnoid space, thus separating the perivascular and subpial spaces from the subarachnoid space [23-27]. Together with basal lamina, the perivascular space is endowed with a thin sheath of leptomeningeal cells that surrounds arterioles and arteries [16]. Perivascular space represents a perilymphatic drainage channel connected to the meningeal interstitial spaces, thus permitting the exchange of fluids and cells between brain and meninges [15]. Leptomeningeal cells forming the perivascular sheath have been characterized by light and electron microscopy and mostly identified as meningeal fibroblasts and meningeal macrophages [21]. Evidence of perivascular nestin-positive cells

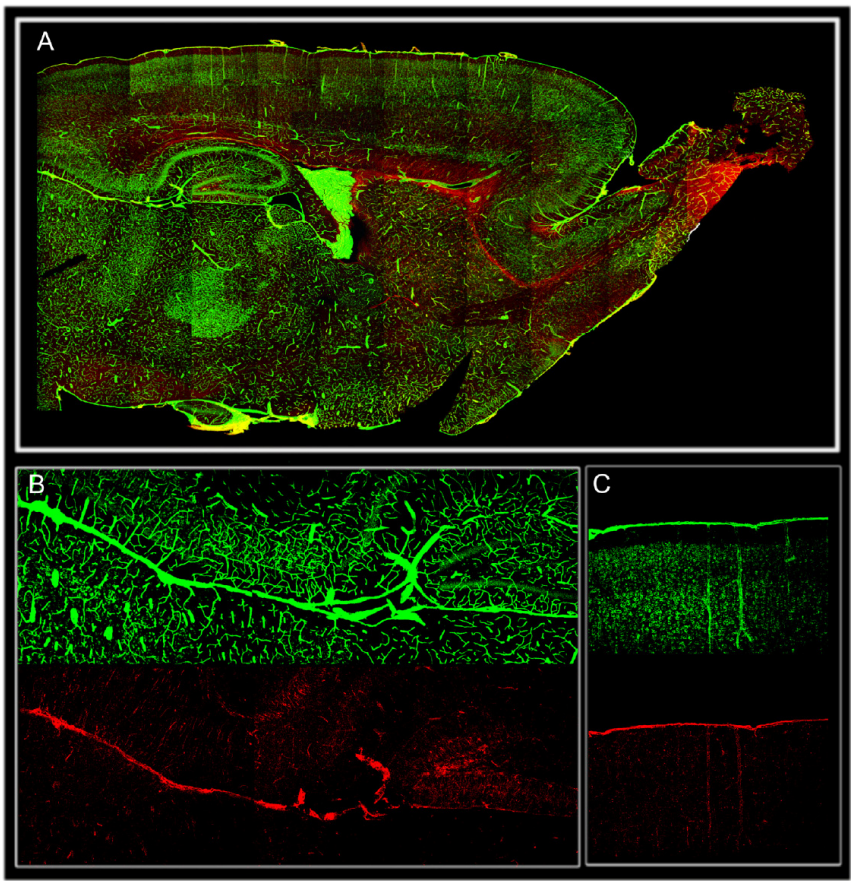

Figure 1. Distribution of brain meninges (laminin green) and nestin positive cells (red) in 15 days postnatal rat brain transversal section. (A). CNS brain meninges meninges cover and penetrate the brain deeply at every level of its organization including sheaths of blood vessels (perivascular space) and projections located underneath the hippocampal formation that continue with the choroid plexus. High magnification showing nestin positive cells associated with meningeal projection underneath the hippocampus (B), and penetrating the cortex as sheath of blood vessels (C). Meningeal stem cells (nestin) appear to be largely diffuse inside the parenchyma.

[28-30], (**Figure 1**) and nestin-positive proliferating endothelial cells [31], have also been reported. Meningeal fibroblasts were observed in the perivascular space of vessels upstream of the capillaries and forming a multilayer around the larger arteries [10, 32]. Perivascular fibroblasts and macrophages form a network by contacting each other with no discontinuity along meninges and the longitudinal axis of the blood vessels [33]. Of note is that the blood-brain-barrier (BBB) is mainly located at the level of the endothelium, thus the extraparenchymal cells residing in the perivascular space are located beyond the BBB [34].

Role of meninges in corticogenesis

Several studies have shown that meninges are essential for the correct development of the CNS. However, all the molecular mechanisms by which meninges and the meningeal cells participate in this process are still to be elucidated.

Meningeal tissue has been shown to be required for encephalon development [4, 35]. The mesodermal components of the forebrain meninges provide the endothelial walls of blood vessels that penetrate the neuroepithelium, while the neural crest originating from the posterior neural folds yields pericytes and connective tissue. The removal of the posterior diencephalic and mesencephalic neural folds prevents meninges development and causes apoptosis of the neuroepithelium of the entire forebrain [4]. Etchevers et al. have shown that the presence of primitive leptomeninges is needed for the survival and subsequent growth of the developing proencephalon. When the neural folds are ablated, paraxial mesoderm can replace the neural crest cells generating primitive leptomeninges that allow encephalon development [4].

Later in development, destruction of the meninges overlying the cerebellum leads to cerebellar hypoplasia, formation of neuronal ectopia and gliosis in the subarachnoid space and reduction of the total number of granular cells [36

-40]. In the hippocampus, destruction of the meninges may induce secondary malformations of the dentate gyrus [41].

Due to their strategic position within the parenchyma and the connection with the vasculature, meninges have the potential to provide short-range factors to neural cells of the developing brain structures [42]. An example is the signal that involves the stromal-derived factor (SDF1)- and CXC chemokine receptor 4 (CXCR4)- dependent pathway. This signal is involved in the homing of various kinds of stem cells as well as in forebrain development [43, 44]. Meninges secrete SDF1 that guides the tangential migration of Cajal-Retzius cells and cortical interneurons along the cortical marginal zone, ensuring their correct distribution during corticogenesis [45-48].

Other morphogens, including retinoic acid, are active at the meningeal level. Indeed, meninges express high levels of retinoic acid, which appears to be critical for early cortical neuron generation [49] and for anterior hindbrain development [50]. Recently, meninges have been shown to be involved in the generation of a cascade of morphogenic signals regulating corpus callosum development; in this case, meninges are involved by producing BMP7, an inhibitor of callosal axon outgrowth. This activity is overcome by the induction of expression of Wnt3 by the callosal pathfinding neurons, which antagonizes the inhibitory effects of BMP7 [51].

Due to the ability to bind several morphogenetic and trophic factors, a special role for corticogenesis is reserved to the extracellular matrix forming the basal membrane. Meningeal cells actively participate in the formation of the extracellular matrix (ECM). Collagens are the most abundant ECM structures in meninges, where the most represented types are I, III, and IV. In addition to collagen, meningeal cells synthesize non-collagen proteins including fibronectin, laminin and tenascin [52]. The pial basal membrane is an important anchor for the endfeet of radial processes that originate from neural progenitors cells residing in the VZ; moreover, it is a physical barrier for the migrating neurons. During cortical and cerebellar development, the radial processes provide a migratory scaffold for neurons that ensures cortical cellular layering. Genetic ablation of components of the pial basal membrane (i.e laminin components alpha1, alpha2 and alpha5) or of the proteins that mediate extracellular matrix attachment leads to a loss of pial integrity, radial endfeet detachment and disruption of cortical and cerebellar histogenesis [53, 54]. Premature detachment of radial endfeet also leads to increased neural progenitor cell death and, eventually, reduced production of cortical neurons [53, 54]. Moreover, mice lacking laminin subtypes show alterations in the distribution of connexin (Cx) 43, a gap junction protein that is expressed in the arachnoid and pia mater of the meninges [55]. It is noteworthy that ablation of this protein, like in the glia-specific Cx43 knockout mice, results in reduction in size of the cerebellum, with appearance of granule cell ectopies and dislamination of Purkinje cells, granule cells, and Bergmann glia [56]. It can be hypothesized that laminins have a role in the functional localization of connexins. Targeted deletion of focal adhesion kinase in meninges elicited altered cortical histogenesis similar to type II cobblestone lissencephaly, with clusters of neurons invading the marginal zone with retraction of radial glial endfeet, midline fusion of brain hemispheres, and gliosis, as seen in congenital muscular dystrophy [57].

Role of meninges in CNS homeostasis

The protective function of meninges was considered the major functional significance of this structure. Indeed, meninges were considered to physically protect the brain from traumas and to be devoid of any functional connection with the brain parenchyma. A continuous mat of extracellular matrix molecules, including laminin, fibronectin, collagens IV, XV and XVIII and heparan sulfate proteoglycans [58], is localized at the surface of the brain as well as around the blood vessels inside the brain. This material was considered to form a sharp interface separating (both anatomically and functionally) the brain parenchyma (neurons and glia) from the extraparenchymal tissues (meninges and vessels).

More in-depth studies of the meninges ultrastructure have contributed to change this limited view of meninges function [21]. Meninges contain a laminin-enriched ECM organized in fractones relevant for sequestering and concentrating growth factors [59] that have the potential to modulate stem cell homeostasis and cortical function. Furthermore, meninges are an

important source of several trophic factors [47-49], including FGF-2 [60], insulin-like growth factor-II [61, 62], CXCL12 [45, 63-65], and retinoic acid [49-51]. Of note is also that numerous growth factors and cytokines, including those promoting stem cell proliferation and differentiation (i.e. FGF2, EGF), are heparin-binding molecules [66, 67] that can bind to the heparan sulfate chains of heparan sulfate proteoglycans that are abundant in meninges. Interestingly, cells of the meninges have been shown to be highly responsive to principal mitogens such as EGF, FGF-2, and BDNF [68, 69]. Heparan sulfate proteoglycans enrichments have been found in regions associated to neural stem cell proliferation [9, 59]. These observations suggest the existence of a functional system involved in the regulation of growth factors in neurogenic regions and in meninges. It has been proposed by Mercier et al. that heparan sulfate proteoglycans regions course as a single anatomical system that comprises the olfactory bulb, the rostral migratory stream, the subventricular zone, the sub-callosum and subcapsule zones and the meninges of the ventral hippocampal neurogenic zone [9].

A further indication that meninges are functionally linked to the neural tissue is the presence of gap junction proteins. Cx43, Cx30 and Cx26 have been found along a network of cells in the meninges and in their projections into the brain, including meningeal sheaths of blood vessels and stroma of the choroid plexus [60, 70-72]. The distribution of these proteins suggests the existence of anatomical and functional interactions between meningeal cells, meningeal-perivascular cells, ependymocytes and astrocytes [60, 71, 73] capable to provide a rapid mean to spread signals. Altogether the data indicate that meninges are an important structure that modulates brain function during embryogenesis and adult life.

Meninges: a novel stem cell niche

Functional complexity linked to cellular complexity

Different cell populations have been described in meninges such as fibroblasts, perivascular and meningeal macrophages, mast cells, pericytes, smooth muscle cells and endothelial cells. Recently, interstitial cells characterized by a small cell body and extremely long, moniliform, cell processes - telopodes named tenocytes [73] have been described. Adding complexity to the potential role of meninges in CNS function was the identification of a stem cell population sharing many features with the bona fide neural stem cells [28, 74-76].

Here, we provide a description of the current knowledge on the *in vitro* cultured meningeal cells, reviewing the established studies on meningeal fibroblasts, the more recent findings on pericytes and boundary cap cells and the latest observations suggesting the presence of a stem cell population in meninges.

Meningeal fibroblasts: The most commonly used markers to identify meningeal fibroblasts are fibronectin, vimentin, chondroitin sulfates (recognized also by CS-56 antibody) and retinaldehyde dehydrogenase type 2 [77]. Meningeal fibroblasts have been shown to play a primary role in the acute and subacute phases of injury-induced parenchymal reaction in CNS, as they promptly infiltrate the lesion site [78, 79]. Here, the reactive astrogliosis and the meningeal cells form a glial-fibroblast interface that produces new basal lamina that, in combination with the glial endfeet, reforms the glia limitans [80, 81]. This process is believed to be essential for restoring the blood-brain barrier and re-establishing CNS homeostasis [80]. In a long series of experiments stretching back for many years, the lesion scar has been identified as one critical element that impedes axonal regeneration in the adult mammalian CNS [82, 83]. After lesion, CNS axons start to sprout over short distances, but almost all of them stop abruptly at the lesion scar border and fail to traverse it [84-86]. *In vitro* cultures of meningeal fibroblasts have been classically used as an *in vitro* model of injury-induced scar, allowing investigation of the mechanisms involved in the formation of the barrier to axon regeneration [80, 87, 88]. Nevertheless, some reports described *in vitro* [89] and *in vivo* [90, 91] axonal growth-promoting properties of cultured meningeal fibroblasts. Moreover, cells from meninges were able to induce neuronal differentiation of embryonic stem cells [92]. As observed *in vivo* at CNS lesion sites [93-96], *in vitro* cultured meningeal fibroblasts are induced by TGF-β1 to produce high levels of ECM components, like Col IV, and various CSPGs, such as biglycan, versican, decorin, neurocan and phosphocan, tenascin-C, semaphorin3A and EphB, while astrocytes are

induced to increase the expression of neurocan, phosphocan and ephrin-B2 [89, 97, 98].

In vitro modelling of the scar confirms that attachment of neurons and extension of neurites are suppressed when they are cultured on a layer of fibroblasts, and they are dramatically diminished if co-cultured on fibroblasts and astrocytes [79, 99]. These results suggest that inhibitory effects are mainly triggered i) by an indirect negative effect of fibroblasts on the growth-promoting abilities of astrocytes and ii) by a direct inhibition of fibroblast on neurite growth mediated by expression of inhibitory molecules such as NG2 and Sema3A [100].

Pericytes: CNS microvascular pericytes reside in the perivascular space, an extrofection of the leptomeninges, and play an important role in vascular homeostasis by producing different ECM components [101, 102]. Pericytes respond to insults to the CNS by secreting different regulatory molecules and migrating into the perivascular space [103] and have been reported to differentiate *in vitro* into macrophage-like cells and osteoblasts. In 2006, Dore-Duffy et al. showed that pericytes isolated from the microvessels of the brain cortex exhibit multipotential stem cell activity [104]. These stem cells express NG2 and nestin and can be cultured *in vitro* as neurospheres. Cultured cells showed cell renewal properties and could be induced to differentiate into pericytes, neurons, astrocytes and oligodendrocytes. Other numerous studies reported pericytes differentiation into mesenchymal lineage cells, such as adipocytes, smooth-muscle cells and endothelial cells [105].

Boundary cap cells: During development, boundary cap (BC) cells regulate the entry of the forming afferent nerve in the spinal cord and cannot be found after postnatal day 6. BC cells are neural crest-derived cells that are found in clusters in the dorsal entry zone and the ventral exit zone of nerve roots in the spinal cord, at the border between the CNS and the PNS in direct contact with the pial lamina [106-109]. BC cells are easily identified in meninges by the exclusive expression of monoamine oxidase type B and, between embryonic days 10.5-15.5, of the zinc finger transcription factor Krox20/Egr2. BC cells have been extracted from meninges of mouse embryo at day 12 [110, 111]. *In vivo*, BC cells generate Schwann cells in the nerve root region and differentiate into nociceptive neurons and glial satellite cells after migration in the dorsal root ganglia [112]; cultured BC cells express both Schwann cell (i.e. Sox9, nestin, Sox2 and Musashi) and neural crest related markers (Sox10, p75, polysialylated neural cells adhesion molecule), suggesting that they are in an intermediate stage of differentiation [113]. *In vitro* cultured BC cells were capable to differentiate in glia, sensory neurons and smooth-muscle-like cells [114]. Moreover, more recent studies showed that cultured BC cells could differentiate *in vitro* into mature Schwann cells capable of remyelinating DRG neurons [115-117]. *In vivo* differentiation potential of cultured BC cells has also been analysed [112, 116, 117]. Interestingly, boundary cap cells have been found to differentiate differently depending on the site of transplantation. They differentiate into neurons and astrocytes in the CNS, into oligodendrocytes in the demyelinated spinal cord and in Schwann cells, glial satellite cells and nociceptive neurons in the DRG.

Meningeal stem/progenitor cells

Supporting the concept of meninges as putative neural stem cell niche, are the peculiar morpho-functional properties of meninges themselves. Indeed, meninges may have the potential to modulate stem cell homeostasis since they contain laminin-enriched ECM organized in fractones [21], N-sulfated heparan sulphate molecules, functional gap junctions and secrete several trophic factors. More recently, Popescu et al. presented evidence for the presence of telocytes in meninges and choroid plexus. Telocytes are interstitial cells that appear to be in close contact with stem cells and to be able to regulate the stem cell niche by generation of intercellular signaling [73]. We have analyzed the leptomeningeal compartment of the rat brain and have identified a nestin-positive cell population in brain meninges of embryonic and adult rodents [28, 74]. Nestin is an intermediate filament of neuroepithelial derivation [118] that has been detected in stem/progenitor cells of neural and non-neural tissues. The cells extracted from the meningeal biopsies could be grown as neurospheres, as in the case of cells extracted from classic neurogenic regions [28]. Meningeal cultured cells could be differentiated *in vitro* and *in vivo* into either neurons (identified by neuronal phenotypic and electrophysiological properties) or into mature MBP-

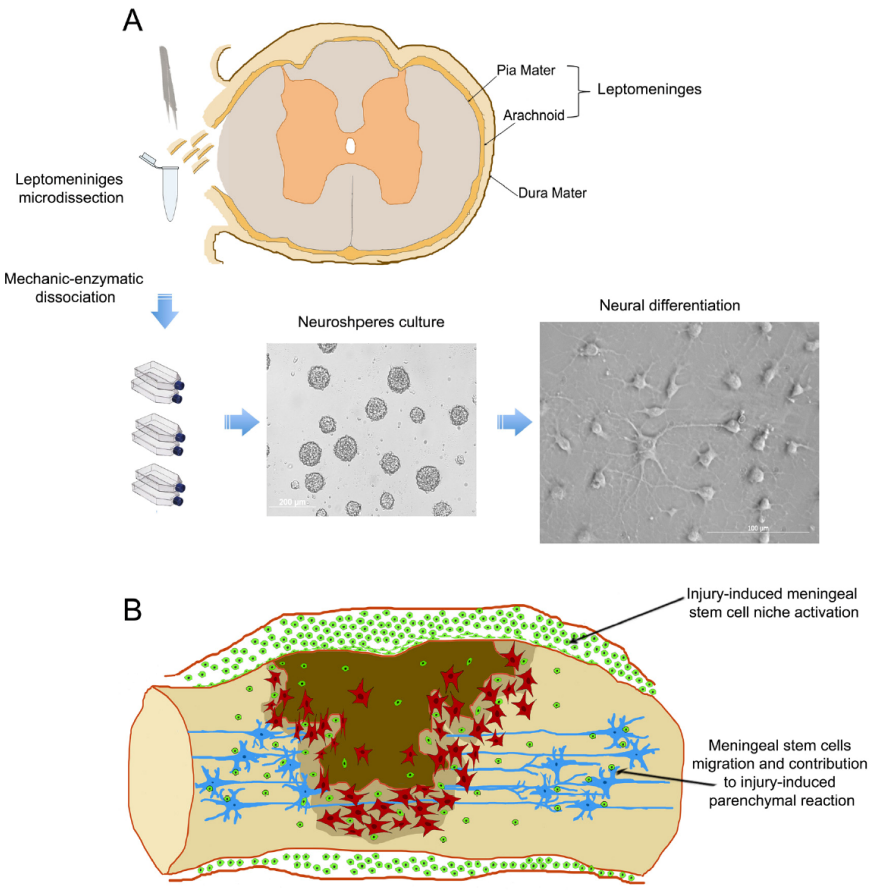

Figure 2. Meningeal stem cells. (A). Meningeal stem cells from adult spinal cord can be microdissected, expanded in vitro and induced to differentiate into neural cells. (B). schematic representation of the activation of the stem cell niche in meninges following spinal cord injury. Meningeal stem cells proliferate, increase in number and migrate inside the parenchyma contributing to the parenchymal reaction.

expressing oligodendrocytes (**Figure 2A**). Nestin-positive cells have been identified also in human encephalic [119] and spinal cord meninges [74], indicating the interspecies relevance of our observation. The data are in agreement with previous indications that NSCs were present in the choroid plexus of the adult rat [120] and that cells from human meninges expressed some neural markers, such as neurofilament protein and neuron-specific enolase when cultured *in vitro*, while they express GFAP after transplantation in rat brains [121-123].

Meninges: an injury responsive stem cells niche

To assess a possible significance of meninges as a niche for stem cells with functional implication in CNS physiopathology, our group investigated the presence of relatively quiescent, mitotically-active transient-amplifying cells and neuroblasts in spinal cord meninges. We found that nestin-positive cells endowed with self-renewal and proliferative properties, and doublecortin (DCX)-positive cells are present in adult spinal cord meninges. A further paradigm to define a stem cell niche is activation by diseases [124-128]. Activation is defined by proliferation and increased number of all the cell subsets [129, 130] participating in a stem cell niche [131] and migration of precursor cells in the parenchyma undergoing reaction. Detailed analysis of changes in gene expression in meningeal spinal cord cells induced by injury showed increase in several stemness-related genes, including Pou5f1/Oct4 and Nanog, and of neural precursor markers, such as Nestin, Dcx, Pax6 and Klhl1 [74]. Moreover, we observed a significant increase of both nestin- and DCX-positive cells in meninges, indicating a general amplification of the meningeal stem cell pools associated to the injury-induced activation [74]. In addition, nestin-negative/DCX-positive cells appeared, suggesting a progression toward the neural fate. We also used an *in vivo* labeling approach to show that meningeal cells migrated and accumulated in the fibrotic scar and were

also present in the glial scar and in the perilesion parenchyma. Interestingly, migrating meningeal cells also penetrated the dorsal horn 30 days after the injury. These data suggest that at least part of the proliferating cells present in the lesioned parenchyma originate from meninges (**Figure 2B**). Moreover, some of the migrating meningeal cells expressed the same markers (nestin and DCX) that are transiently expressed by neural precursors within classic neurogenic niches of the embryo and the adult brain, providing new insights into the complexity of the parenchymal reaction to a traumatic injury [74]. Almost at the same time, Nakagomi et al. demonstrated that the leptomeninges exhibit neural stem/progenitor cell (NSPC) activity in response to ischemia in adult brains [75]. Pial ischemia-induced NSPCs (iNSPCs) expressed the NSPC marker nestin, formed neurosphere-like cell clusters with self-renewal ability, and differentiated into neurons, astrocytes, and oligodendrocytes [75], indicating that they have stem cell capacity similar to other NSPC types. Moreover, the same group shows that leptomeningeal cells in post-stroke brain express the immature neuronal marker doublecortin as well as nestin [76] and that these cells can migrate into the post-stroke cortex.

These new findings highlight a new role for leptomeninges in CNS repair in response to CNS injury and suggest the existence of a new stem cell niche in the meninges that participates in the reaction occurring in the parenchyma following injury [29]. Although the *in vivo* role and the fate of the meningeal stem/precursor cells remain to be fully elucidated, these observations may have relevant consequences for understanding the mechanisms of stem cell activation in CNS diseases and the nature and origin of neural cell precursors appearing in ectopic non neurogenic regions of the brain. The superficial location and widespread distribution of meninges make this site an attractive source of neural cell precursors to be used for regenerative medicine applied to pathologies of the spinal cord and/or the brain, especially considering their possible use in an autologous setting.

Conclusion

Data in literature indicate a complex role of the meninges in CNS homeostasis.

The idea that the continuous membranous mat of extracellular matrix localized at the surface of the brain and spinal cord as well as around the blood vessels in the CNS, forms a sharp interface separating (both anatomically and functionally) the brain parenchyma (neurons and glia) from the extraparenchymal tissues (meninges and vessels) is changing. Meninges are considered to form a functional network together with parenchymal tissue contributing to CNS physiology and injury-induced reactions.

Primitive meninges form as early as the neural tube develops. They are necessary for the development of the whole forebrain and for the generation of the primitive brain vasculature. In adult, meninges cover and penetrate the CNS deeply at every level of its organization, including formation of large projections between major brain structures. Moreover, all the major arteries supplying the brain pass through leptomeninges and form branches while penetrating the cortex. Leptomeninges form a complex microenvironment by producing trophic factors and extracellular matrix components that have key functions for the normal cortex development.

On top of these anatomical considerations, our discovery of a new stem cell population endowed with neural differentiation potential in the meninges sheds a new light on meninges function in physiology and in pathology. This stem cell population shows *in vivo* self renewal and proliferation properties that are activated by spinal cord injury and brain stroke. Meningeal activated stem/precursor cells are able to migrate to the parenchyma contributing to parenchymal reaction, providing new insights for understanding the complexity of the parenchymal reaction to injury. Altogether, the data suggest that meninges are a functional stem cell niche. The nature and the origin of these meningeal stem/precursor cells have to be further characterized as far as their potential contribution to the neural tissue both in physiological and pathological conditions. Given their distribution, meninges may be a strategic net helping intracerebral migration and distribution of activated precursor cells at specific sites. Meninges are also more accessible than other neural stem cell niches, an aspect that has interesting implication for sampling of NSCs for regenerative medicine.

In conclusion, we reviewed the several functions of meninges showing that meninges are not merely a protecting sac coverings the CNS but

form a functional syncytium with the neural tissue. Further studies are needed to clarify the presence and the role of the stem cells in meninges during development and the possible function of meninges as anatomical net for stem cell migration to sites of integration into the normal and injured tissue [29]. This will open new prospectives for the pharmacological modulation of meningeal endogenous stem cells for the regenerative therapies of neurodegenerative diseases.

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