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We've got you "covered": how the meninges control brain development

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The meninges have traditionally been viewed as specialized membranes surrounding and protecting the adult brain from injury. However, there is increasing evidence that the fetal meninges play important roles during brain development. Through the release of diffusible factors, the meninges influence the proliferative and migratory behavior of neural progenitors and neurons in the forebrain and hindbrain. Meningeal cells also secrete and organize the pial basement membrane, a critical anchor point for the radially-oriented fibers of neuroepithelial stem cells. With its emerging role in brain development, the potential that defects in meningeal development may underlie certain congenital brain abnormalities in humans should be considered. In this review, we will discuss what is known about assembly of the fetal meninges and review the role of meningeal-derived proteins in mouse and human brain development.

Origin and Structure of the Fetal Meninges

The first, primitive layer of meningeal cells is identifiable early in neural development: in chick, at HH15 (Embryonic day or E2) [1], in mouse between E9-E10 [2] and in human, Carnegie stage 15 or ~4th gestational week [3]. In the forebrain, this initial layer of meningeal cells is part of a wave of rostrally migrating cranial neural crest cells originating from the diencephalic neural crest [4]. In contrast, the meninges surrounding the midbrain, hindbrain, and spinal cord originate from the cephalic and somatic mesoderm [5-7] (Fig. 1A). This first group of meningeal cells ultimately becomes part of the leptomeninges, consisting of the two inner layers - the pia and arachnoid. In embryos, the leptomeninges are a loose network of cells lying in close contact with the surface of the brain, adjacent to the glial limitans, and intermingled with blood vessels of the perineural vascular plexus (Fig. 1B). The leptomeninges are first identifiable in human embryos between stages 17 and 18 [3] and ~E13 in mouse [2]. The outermost meningeal layer, the dura, forms between the leptomeninges and the calvarial mesenchyme, from which the calvarial bones will eventually form (Fig. 1B). Cells of the cephalic dura are first seen in mouse embryos at ~E14 [8] coinciding with the initial apical expansion of the calvarial bones [9,10].

Very little is known about regulation of meningeal development. Some insights into meningeal assembly came from studies showing that loss of the transcription factor Foxc1 disrupts formation of the forebrain meninges. A spontaneously occurring *Foxc1* mouse

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mutant (the *congenital hydrocephalus* or *ch* mutant) was noted to have marked thinning of the meningeal layer in the initial reports describing these mice [11,12]. Years later, analysis of the *ch* mutant and mice with targeted disruption of Foxc1 (*Foxc1-lacZ*) confirmed that forebrain arachnoid and dural layers were absent except over the ventral surface [13,14*, 15**]. While the exact role of Foxc1 in meningeal development is unclear, the meningeal phenotype in a less affected *Foxc1* hypomorphic mutant (*Foxc1-hith*) [8] suggests that it regulates meningeal cell migration. In *Foxc1* hypomorphs, the meninges are missing only from the more dorsal aspects of the forebrain and even in the *Foxc1* hypomorph-null hybrid ($Foxc1^{hith/lacz}$) the arachnoid and dural layers extend partially around the forebrain [15**]. This suggests that, at least in the forebrain, meningeal development may involve a ventral-dorsal wave of meningeal cell migration and that Foxc1 is critical for this process.

Secreted factors from the meninges regulate neural migration and positioning

The meninges, with their close proximately to the developing brain, are strategically positioned to provide short-range cues to neural cells located in the outer layer of developing brain structures. One example of this type of signal is Cxcl12 (aka SDF-1), which mediates chemoattraction of multiple cell types via binding to its receptors Cxcr4 and Cxcr7 (for review see [16]). In the forebrain and cerebellum specifically, meningeal-derived Cxcl12 plays an important role in neuronal migration and cell positioning.

Subpial migratory routes regulated by Cxcl12 are a common theme in development

During forebrain development rapid, tangential dispersion of neuronal subtypes in the subpial marginal zone (MZ) is a recurring program for distributing cells over long distances. Cajal-Retzius (CR) cells are the first to utilize this migratory route, originating from the edges of the cortex (the cortical hem, pallial-subpallial border and septum) then migrating tangentially in the MZ to cover the cortex [17-19] (Fig 2A). CR cells remain in the MZ throughout cortical development where they produce and secrete the glycoprotein reelin, an important migratory modulator critical for correct laminar positioning of neurons in the cerebral cortex (for review see [20]. Removal of the meninges from early forebrain explants halts migration of CR cells within the MZ, indicating that the meninges produce chemoattractive signals for CR cells [21**], and inhibitors of Cxcr4 signaling blocks CR cell chemotaxis toward the meninges in vitro [21**,22]. *Cxcl12* and *Cxcr4* null mutants have incomplete reductions in CR cell positioning in the forebrain marginal zone [21**, 22,23], indicating that other factors from the meninges or the brain may also be involved in regulating CR cell migration in the MZ.

Slightly later in forebrain development, meningeal Cxcl12 guides tangential migration of inhibitory interneurons within the dorsal forebrain. Interneurons are born in the ventral forebrain and subsequently form two migratory streams as they enter the dorsal forebrain: the MZ stream adjacent to the Cxcl12-expressing meninges and a deeper route through the subventricular zone (SVZ) where Cxcl12 is expressed by SVZ intermediate progenitors [24-26] (Fig. 2B). After exiting the stream, interneurons migrate radially to their final position in the forming cerebral cortex. Loss of responsiveness to Cxcl12 mediates exiting of interneurons from the migratory stream [26], and the interneuron migratory streams in *Cxcr4*, *Cxcr7* and *Cxcl12* null mutants are disorganized with premature exit from the streams into the cortical plate [23-28]. Disrupted interneuron migration caused by loss of Cxcl12 signaling negatively impacts interneuron number and positioning in the adult cortex and ultimately affects the inhibitory tone in cortical circuits [25-28].

Meningeal Cxcl12 mediates interaction of neural progenitors with stem cell niches

Both homing and retention of cells in a specific location is frequently mediated by a strong chemoattractive signal like Cxcl12. In addition to the example of CR cells and interneurons (discussed above) there are two instances where Cxcl12 regulates the localization of neural precursors cells adjacent to the meninges, possibly to maintain their proximity to the appropriate stem cell niche. In both the developing cerebellum and dentate gyrus, granule cell progenitors are positioned within a neurogenic zone by meningeal Cxcl12. During cerebellar development, granule cell progenitors (GCP) proliferate in the outer external granule cell layer (EGL) at the edge of the cerebellar folia, then move into the inner EGL as post-mitotic cells and finally migrate inward on Bergmann radial glia to their final position in the internal granule cell layer [29]. In the cerebellum of both *Cxcl12*-null and *Cxcr4*-null mouse mutants, the GCP are displaced inward and the proliferative capacity of the progenitors is diminished [30,31], indicating that meningeal Cxcl12 is involved in retaining GPCs in the superficial layer of the EGL. In addition, there is evidence in cerebellar GCPs that Cxcl12 cooperates with Sonic Hedgehog as a mitogenic stimulus in these cells while they are adjacent to the meninges [32].

Similarly, during dentate gyrus morphogenesis, Cxcr4-expressing granule cell progenitors migrate from the dentate primordium to the forming dentate gyrus along the Cxcl12-enriched meninges (Fig. 2C). This migratory stream also functions as a temporary, subpial layer of proliferating dentate progenitors [33*]. In *Cxcr4*-null mice the migratory stream is disrupted and the transient neurogenic zone fails to form adequately [33*,34,35]. This results in premature differentiation of dentate granule cell precursors and the resulting post-mitotic granule cells are found ectopically within the migratory stream. Thus, Cxcl12-signaling in both the cerebellum and dentate gyrus is required for proper positioning of granule cell progenitors, and ultimately, for maintaining their proliferative capacity either due to direct Cxcl12 signaling in the progenitors or in cooperation with other niche-derived factors, e.g. Sonic Hedgehog.

Retinoic acid produced by the meninges regulates forebrain and hindbrain development

Retinoic acid (RA) is a lipophilic, small molecule critical for early events in CNS development, including neural tube closure and early forebrain patterning [36,37]. The meninges express high levels of RA synthesizing enzymes [38,39] and have proven to be in important source of this morphogen during brain development.

Neocortical development starts with an expansion phase where radial neural progenitors go through symmetric, self-renewing divisions. As cortical neuron generation begins, progenitors switch to asymmetric divisions to produce neurons directly or indirectly through intermediate progenitor populations (see review see [40]). The identity or even the existence of molecules responsible for the “neurogenic switch” is a longstanding topic of debate, but recent work using the meninges-deficient *Foxc1* mutants indicates that retinoic acid made by the meninges is a major part of the switch driving the neurogenic decision [15**] (Fig. 3B). In *Foxc1* mutants, there is an overabundance of symmetric divisions at the expense of neuron production resulting in a long, thin neocortex. The subpopulation of meningeal cells expressing RA synthesizing enzymes are partially or completely missing in the various *Foxc1* mutants, indicating a local deficiency in RA production. Indeed, supplementation with exogenous RA rescues the neuron generation defects in the *Foxc1* mutants. Interestingly, RA synthesizing cells appear in the forebrain meninges in a lateral-to-medial direction between E12-E13, corresponding to both the timing and the lateral-to-medial birth of the first cortical projection neurons. This, in conjunction with the *Foxc1* mutant

phenotype, is compelling evidence that RA from the meninges is an important component of the neurogenic switch.

Meningeal-derived RA may also play a role in anterior hindbrain development. RA signaling, as indicated by the *RAREhasp68-lacZ* reporter line, in the developing anterior hindbrain is found in neurons migrating from the dorsal precerebellar neuroepithelium to form the ventral pontine nuclei [41]. This dorsal-to-ventral migratory stream is located at the surface of the hindbrain, immediately below the RA-producing meninges. Though meninges-free hindbrain explants indicate that RA signaling in pontine nuclei neurons is dependent on RA from the meninges, it is unclear mechanistically how RA regulates the migration or maturation of this cell population.

Maintenance of the pial basement membrane by the meninges

Immediately below the pial meningeal layer is the extracellular matrix-enriched basement membrane (BM). The pial BM acts as both an anchor point for the endfeet of radial processes that originate from neuronal progenitors cells residing in the ventricular zone (VZ) and as a physical barrier to migrating neurons. During both cortical and cerebellar development, the radial processes provide a migratory scaffold for neurons that helps ensure correct cellular layering. Genetic ablation of components of the pial BM [42,43] or the proteins that mediate cell-ECM attachment [44-47] leads to loss of pial BM integrity, radial endfeet detachment, and disruption of cortical and cerebellar histogenesis. Premature detachment of radial endfeet also leads to increased neuronal progenitor cell death and, subsequently, reduced production of cortical neurons [48].

The first studies connecting the meninges to BM maintenance used focal, chemical ablation of the meninges from the surface of the cerebellar cortex to show breakdown of the pial BM followed by BM restoration when meningeal cells repopulated the lesion site [49]. The meninges may regulate pial BM integrity via cell-ECM adhesion, as indicated by the breakdown in the BM following conditional ablation of focal adhesion kinase from meningeal fibroblasts [46*]. Further studies in which ECM and cell-ECM proteins are conditionally ablated from the meninges will shed light onto the specific function of the meninges in pial BM maintenance.

More recently, BM defects in the neocortex have been observed in conjunction with cellular defects in the meninges, as is the case with the *Foxc1* mutants [8,50] and in *Zic1/3* double mutants [51]. In *Foxc1*-null mutants, there is a progressive breakdown in the pial BM from mid-corticogenesis onward resulting in severe disruption in the radial glial scaffold and cortical organization [50]. Zic1 and Zic3 are zinc-finger transcription factors that are expressed in the meninges in addition to subsets of cells in the developing forebrain [52]. *Zic1/3* mutants have reduced expression of meningeal genes, like Cxcl12 and Foxc1, and meningeal-derived laminin [51]. In these mutants, the pial BM is disrupted and there is evidence of radial glial endfeet detachment. Collectively this suggests that primary meningeal defects can lead to disruption of the pial BM, and ultimately, lead to defects in cerebral cortical development.

Meninges and neurodevelopmental disorders: potential connection?

Meningeal-derived factors are involved in several, critical developmental events in the brain. This raises the possibility that defects in meningeal development or function, either through genetic mutation or through damage to the meninges in utero, may underlie certain neurodevelopmental disorders in humans. Recently, some cases of Dandy-Walker Syndrome, characterized by cerebellar hypoplasia and hydrocephaly, were linked to *FOXC1* heterozygosity with small chromosomal deletions (6p25.3-*FOXC1*) or loss-of-function

mutations [53**]. In *Foxc1*-null mouse embryos, aberrant migration and differentiation of cells originating from the rhombic lip and roof plate, two transient hindbrain structures that supply cells to the developing cerebellum, underlies the defects in cerebellar development. Unlike the forebrain meninges, the meninges over the hindbrain appear intact, suggesting that Foxc1 in hindbrain meninges regulates expression of secreted factors required for cerebellar development. In addition, almost half the 6p25.3-*FOXC1* patients showed evidence of cortical meningeal defects, specifically defects in the midline; this is the same area of the meninges that is affected in *Foxc1* hypomorph mutants, which like humans with *FOXC1* mutations retain some Foxc1 protein expression, suggesting that the midline cortical meninges are uniquely vulnerable to loss of *Foxc1*.

Disruption of the meninges or meningeal-derived proteins in mice often results in disorganized cytoarchitecture and ectopic neuronal populations, most often in the cerebral cortex. This type of cortical dysplasia in mouse mutants resembles the type 2 lissencephalies seen generally in the cortex associated with congenital muscular dystrophies (CMDs) and more focally in sporadic cortical dysplasia seen in some individuals with intractable epilepsy. In the case of CMDs, like Walker-Warburg Syndrome, Fukuyama Muscular Dystrophy and Muscle-Eye-Brain disease, loss of pial BM integrity and emigration of neural tissue into the overlying meninges is observed in post-mortem analysis [54,55]. Though cytologic defects in the meninges have not been systematically examined in CMD patients or in animal models of CMD, it is possible that the genetic defects underlying CMDs, which include aberrant glycoslyation of α-dystroglycan, disrupt meningeal maintenance of the BM. Unlike CMDs, focal cortical dysplasias encompass a wide variety of cortical defects, including heterotopic cell clusters and disorganized cortical layering, seen in both radiological and histological studies of epileptic patients (for review see [56]. The heterogeneity of this disorder suggests a varied etiology, including the potential that focal meningeal defects, caused by in utero infection or hemorrhage, may disrupt developmental processes in the underlying cortical region.

Conclusions

Studies over the last few years have made clear that the meninges are far more than strictly a protective layer in the adult tasked with the resorption of circulating CSF. It is now clear that the forebrain and hindbrain meninges serve as a signaling center coordinating developmental events between the cortex and the skull by releasing a variety of secreted factors that instruct surrounding tissues in the course of their developmental programs. In the case of the forebrain, where the meninges is of cranial neural crest origin, the meninges have likely played an important role during the evolution of the vertebrate head helping to coordinate the structure of the skull and the brain. It is also clear that disruption of meningeal function either generally or focally can lead to significant disruption of brain development. Future work will inevitably expand our understanding of the human syndromes where brain malformations are caused primarily by defects in meningeal development.

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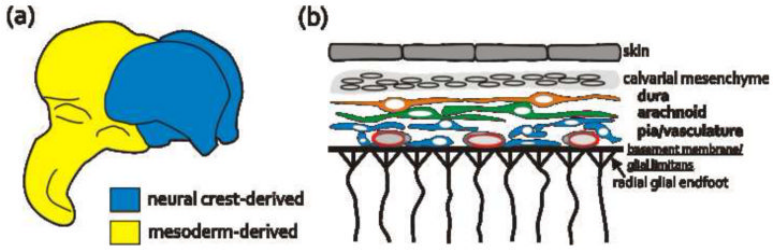

Figure 1.

Origin and structure of the fetal meninges

(a) The meninges surrounding the forebrain are neural crest-derived (blue) whereas the meninges covering the rest of the brain and spinal cord originate from the somatic mesoderm.

(b) The pial meningeal cells and blood vessels are in close contact with the pial basement membrane, the attachment point for radial glial endfeet. The two outer meningeal layers, the arachnoid and dural layers, are single layers of cells beneath the calvarial mesenchyme.

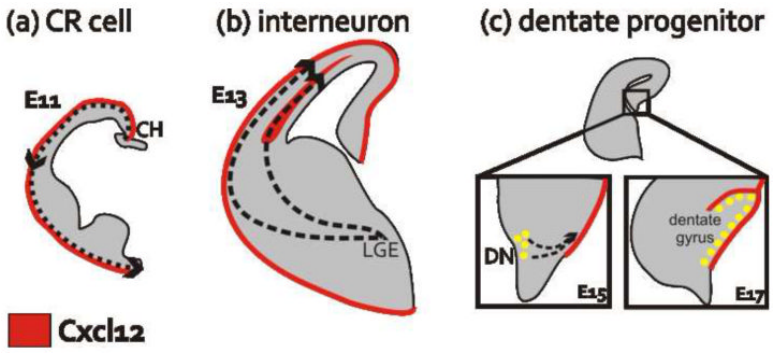

Figure 2.

Subpial migratory routes mediated by meningeal-derived Cxcl12

(a) Beginning at E11 in the mouse telencephalon, some CR cells originate in the midline cortical hem (CH) then migrate at the periphery, adjacent to the meninges, to cover the entire surface of the forebrain.

(b) Starting at E13 interneurons migrate from their birthplace in the lateral ganglionic eminence (LGE) to the cortex where they utilize two Cxcl12-lined migratory streams, a subpial route and a deeper path in the SVZ.

(c) At the beginning of dentate morphogenesis (E15), dentate progenitors migrate away from the neuroepithelium at the dentate notch (DN) toward the Cxcl12-enriched meninges. Two days later, the dentate progenitors are arranged in a subpial neurogenic niche.

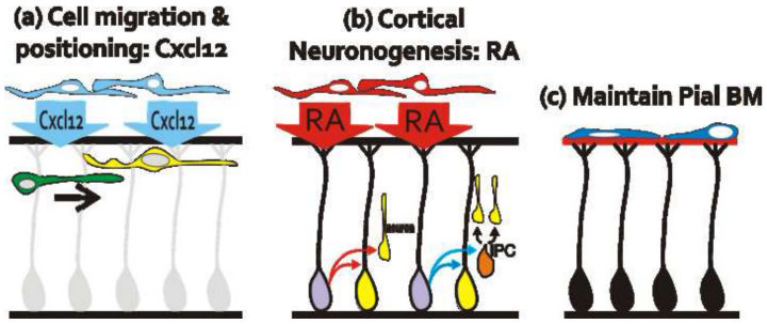

Figure 3.

Three main functions of the meninges during brain development.

(a) Through release of the chemokine Cxcl12, the meninges regulate cell migration and positioning of multiple neuronal populations throughout development.

(b) During cortical development, RA produced by the meninges induces neural progenitors in the cerebral cortex to produce neurons directly or indirectly through an intermediate progenitor cell (IPC).

(c) Meningeal fibroblasts in the inner pial layer organize and maintain the BM, a critical attachment point for radial glial endfeet