The cerebral spinal fluid (CSF) flow tract is a vital lifeline for supplying the brain with essential nutrients and growth factors throughout development and into adulthood. At the same time, the brain exercises constant control to ensure that the flow of CSF is homeostatic. CSF is secreted by the choroid plexus, failure to drain the CSF at the subarachnoid space, and the blockage of CSF flow through the narrow Sylvian aqueduct, which is situated between the third and fourth ventricles and into the subarachnoid space before being drained into the venous circulation (80). Failures within this cerebral irrigation network can lead to a buildup of CSF in the ventricular cavities of the brain, a condition known as hydrocephaly, which is fatal without surgical intervention. Hydrocephalus can result from an overproduction of CSF by the choroid plexus, failure to drain the CSF at the subarachnoid space, and the blockage of CSF flow through the narrow Sylvian aqueduct, which is situated between the third and fourth ventricles. Indeed, stenosis of the Sylvian aqueduct is considered the primary cause of congenital hydrocephalus, which is quite frequent, occurring with an incidence of 0.1–0.3% of live births (80). The reasons for this disease are quite heterogeneous and have been linked to a number of genetic mutations, both autosomal and X-linked (112). What is intriguing, though, is that many of these mutations impinge on the development or function of the subcommissural organ (SCO) and the ventricular ependymal (vel) cells that collectively facilitate the flow of CSF through the confining canals of the ventricular system (Table 1).

The goal of this review is to summarize the molecular mechanisms that cause 1) the SCO to be absent or disorganized, 2) an inability of the SCO to properly secrete glycoproteins, 3) primary ciliary dyskinesia (PCD) of the ependymal cells, and 4) denudation of the neuroepithelium. Although it should be noted that not all SCO/vel defects have been proven to precede the onset of hydrocephaly, indeed it is the aberrant execution of these diverse molecular pathways that can lead to stenosis of the aqueduct and contribute to communicating or non-communicating hydrocephalus.

Underlying the Etiology of Hydrocephalus

The heterogeneous nature of congenital hydrocephalus has hampered our understanding of the molecular basis of this common clinical problem. However, disease gene identification and characterization of multiple transgenic mouse models has highlighted the importance of the subcommissural organ (SCO) and the ventricular ependymal (vel) cells. Here, we review how altered development and function of the SCO and vel cells contributes to hydrocephalus.

The SCO-ping Out the Mechanisms Underlying the Etiology of Hydrocephalus

The SCO is a small secretary gland positioned in the dorsal caudal aspect of the third ventricle underneath the posterior commissure. The SCO is derived from the neuroepithelial cells that line the humors of the dorsal-caudal aspect of the diencephalon. This anatomic region is also described as the prosomere 1 (P1), demarcated by the pineal gland and the mesencephalon. The primitive epithelial progenitors of the presumptive SCO are driven toward a specialized secretory ependymal cell fate in response to the inducive Wnt and Bmp signals emanating from the roof plate of the diencephalon boundary (FIGURE 1A). Indeed, the roof plate acts as an important organizing center for the secretion of these morphogens that are crucial for establishing the dorsal-lateral identity along the central nervous system (CNS) (31, 58, 59). Although malformation of the SCO during gestation leads to ventricular dilation and aqueductal stenosis before birth (FIGURE 1, B AND C) (32, 80), the involvement of specific factors has been slowly elucidated over the past decade through the analysis of mutant mouse models.

One such protein is Mx1, a critical factor involved in dorsal neural patterning (3, 84). Mx1 along with Mux2 and Mux3 form a family of homedomain transcriptional repressors (18, 96, 111). The earliest expression of Mx1 is observed at the neural fold stage, along the boundary of the neural plate (17, 38). Upon closure of the neural tube, Mx1 is prominently expressed along the entire length of the dorsal midline of the neural tube. Mx1 is also expressed in the SCO, choroid plexus (CP), and the habenula in the third ventricle (84). Bach et al. clearly demonstrated that homozygous mutants for Mx1 were unable to sustain Wnt1 and Bmp expression in the dorsal midline of P1, and histological analysis demonstrated the absence of a SCO and a poorly organized posterior commissure (3, 84). Loss of morphogen induction in P1 consequently downregulated cell fate markers such as P1 consequently downregulated cell fate markers such as P1 consequently downregulated cell fate markers such as P1 consequently downregulated cell fate markers such as P1 consequently downregulated cell fate markers such as...
Table 1. Mutations that lead to hydrocephaly in the mouse

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description/Function</th>
<th>SCO/Neuroependymal Phenotype</th>
<th>References</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Developmental defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>En-1</td>
<td>Transcription factor</td>
<td>Ectopic expression leads to SCO agenesis, ependymal differentiation defects in CP/SCO</td>
<td>60</td>
</tr>
<tr>
<td>Hha</td>
<td>Unknown</td>
<td>SCO agenesis, ependymal differentiation defects</td>
<td>24</td>
</tr>
<tr>
<td>Max</td>
<td>Transcription factor</td>
<td>SCO agenesis, neuroependymal derudation</td>
<td>3, 29, 84</td>
</tr>
<tr>
<td>Pax3</td>
<td>Transcription factor</td>
<td>SCO agenesis</td>
<td>27</td>
</tr>
<tr>
<td>Rfx4_v3</td>
<td>Transcription factor</td>
<td>SCO agenesis, neuroependymal defects</td>
<td>2</td>
</tr>
<tr>
<td>Wnt1</td>
<td>Secreted morphogen</td>
<td>SCO agenesis, severe midline structure defects</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Signal transduction defects</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Pac1</td>
<td>G-protein coupled receptor</td>
<td>Overexpression leads to SCO agenesis, ependymal cilia are short and disorganized</td>
<td>50</td>
</tr>
<tr>
<td>Socs7</td>
<td>Suppressor of cytokine signaling</td>
<td>SCO cellular structure is disorganized</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Cilia structure/function defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydn</td>
<td>Central pair-dynein adaptor</td>
<td>Missing central pair projection; ciliary motility defects</td>
<td>22, 53</td>
</tr>
<tr>
<td>FoxII/IIH-4</td>
<td>Transcription factor</td>
<td>Ciliogenesis defects</td>
<td>13, 20</td>
</tr>
<tr>
<td>Mshh5</td>
<td>Dynamin heavy chain</td>
<td>Outer dynein arm missing, ciliary motility defects</td>
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</tr>
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<td>Pdcd1</td>
<td>Unknown, may bind to central pair</td>
<td>Ciliary motility defects</td>
<td>55</td>
</tr>
<tr>
<td>Polari/188</td>
<td>IFT particle protein</td>
<td>Epimembrane cells are shorter, disorganized, and beat asynchronously, CP defects</td>
<td>6</td>
</tr>
<tr>
<td>PolA</td>
<td>DNA repair polymerase</td>
<td>Inner dynein arm abnormalities, ciliary motility defects</td>
<td>47</td>
</tr>
<tr>
<td>Spag6</td>
<td>Central pair-dynein adaptor</td>
<td>Ciliary motility defects, Spag16 inactivation increases severity of hydrocephalus</td>
<td>93, 116</td>
</tr>
<tr>
<td></td>
<td>Cell adhesion defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1-cam</td>
<td>Cell adhesion molecule</td>
<td>Defects in neuronal neurite outgrowth, neuroependymena appear normal</td>
<td>90</td>
</tr>
<tr>
<td>Nmhc-1b</td>
<td>Component of apical cell adhesion complex</td>
<td>Neuroependymal derudation</td>
<td>61, 104</td>
</tr>
<tr>
<td>Napa/o-Snap</td>
<td>Apical transporter of cell adhesion molecules</td>
<td>Neuroependymal derudation with mutation that causes reduced expression of protein</td>
<td>19, 36</td>
</tr>
</tbody>
</table>

*Unless otherwise stated, all mutations are inactivating.

As Ptk6, Pax7, and Lim1, whereas the P2 marker Gln2 remained unaffected. The Max1 mutant mice developed hydrocephaly, and the interactions of Max1 with Wnt1 and Pax3 are corroborated by similar hydrocephalic phenotypes in Wnt1 and Pax3 alleles of homozygous and heterozygous mice (27, 60). It is also possible that Max1 may regulate genes that maintain homeostasis in the mature SCO ependymal cells. Max1 is already known to influence a diverse array of gene expression programs during neuronal development (85). Moreover, the residual ependymal cells of the SCO were not immunoreactive with anti-Reissner’s fiber serum (AFRU), suggesting the absence of the SCO were not immunoreactive with anti-Rfx3–/– mice, congenital non-communicating hydrocephaly was observed in the heterozygous condition (11). The agenesis of the SCO was a common feature found in both Rfx3–/– and Rfx4_v3–/– mice (2, 11). The absence of a functional SCO was ascertained by the degree of immunoreactivity using anti-S-COX spindlin (Rfx4_v3–/–) and anti-RFX (Rfx3–/–) in the presumptive SCO region. In both studies, the degree of immunoreactivity was significantly reduced. Although both mouse knock-out models resulted in the absence of a functional SCO, an intriguing observation was reported in the case of the Rfx3 phenotype. The Rfx3–/– mice appear to have an overall dysfunc-

A molecular role for Rfx proteins in the development of the di-mesencephalic region suggests the involvement of intracellular signaling pathways, such as those involving the G-protein coupled receptor (GPCR) family. Rfx transcription factors interact with other members of the Rfx family, forming homo- or heterodimers to regulate gene expression. In the case of Rfx4, a recent microarray study showed that Rfx4 regulates genes involved in neurogenesis and neurodevelopment, including those encoding transcription factors and cell adhesion molecules.

FIGURE 1. Growth and development of the ventricular system. A: sagittal section depicts the morphological changes that occur in the ventricular system during development. B: coronal section shows the relative position of the ventricles and the neighboring brain structures. C: transverse section highlights the fission of the lateral ventricles. D: oblique section illustrates the complex relationship between the ventricles and the surrounding neural tissue.
In the case of the Rfx4_v3 studies, homozygous knockouts of Rfx4_v3 strongly suggest its role as a critical mediator of an earlier dorsal midline patterning decision. Rfx4_v3−/− mice were embryonic lethal due to catastrophic midline defects. Rfx4_v3−/− telencephalon at E12.5 were characterized by hypoplasia of the dorsal midline and adjacent cerebral cortex. The dorsal midline defect was also evident due to the down regulation of Wnt7a and Wnt7b in the cortical hem, a midline structure that normally produces these transcripts (11). A recent microarray experiment identified components of the Wnt, Bmp, and retinoic acid signaling pathways to be potential targets of Rfx4_v3 in E10.5 brains (110).

From the studies described above, tight regulation along the dorsal midline through Wnt and Bmp signaling pathways is an important regulatory mechanism for the proper development of the differentiated ependymal cells of the SCO and for preventing the onset of hydrocephalus. Indeed, this is also noted in mice that ectopically express Engrailed-1 (En-1), a transcription factor that is important for establishment of the mid-hindbrain boundary, since these animals were presented with hydrocephaly and SCO agenesis in the P1 domain (60). Similarly, a recent report by Dietrich et al. produced a mouse model linking the Huntington's disease gene (Hdh) to congenital hydrocephaly (24). In this study, a mid- to hindbrain-specific inactivation of Mdh was generated by crossing Hdh(Cre) mice with animals that express Cre under the control of a Wnt regulatory element. The Wnt1-Cre;Mdh(Cre) mice came to term but displayed reduced growth and progressive wasting due to the build up of excessive CSF, expansion of the ventricles, and the loss of cortical tissue. Histology revealed expansion of the lateral ventricles by E17.5, indicating the congenital nature of the hydrocephaly. Despite the complete absence of huntingtin (htn) in the mutant CP, no gross structural defects were observed using immunohistochemistry for a variety of markers (24). The effect of htn loss was more overt in the mutant SCO. Mutant SCO was ~40% the size of the controls. Serial coronal sections depicting a hydrocephalic E18.5 mouse brain. Mutations in genes that regulate the tightly controlled patterning in the dorsal midline of P1 lead to SCO malformation and congenital hydrocephaly. Wnt1, Meox1, Rfx3, Rfx4_v3, Pads, and Engrailed have been demonstrated to be critical players in this process. Manipulation of these genes frequently leads to agenesis of the SCO (dotted area) and the stenosis of the SA. The closure of the SA causes an accumulation of the CSF resulting in dilatation of the III-V and LV. The enlargement of the ventricles results in a secondary loss of cortical tissue and a characteristic doming of the cortex.
sections revealed that only the rostral portion of the SCO appeared properly differentiated as detected by SCO-spondin staining. Moreover, caudal to the SCO domain, ectopic SCO-spondin expression was detected in the ependymal lining of the Sylvian aqueduct (24). Further characterization of these mice is needed to determine whether the defect lies in inappropriate secretion of glycoproteins from the SCO or altered function of the vel cells lining the aqueduct. Nonetheless, these findings suggest that htt has a role in regulating the function of specialized ependymal cells. Taken together, the proper development of the SCO is essential for CSF circulation through the narrow Sylvian aqueduct, and other factors that regulate dorsal patterning at or near the mid-hindbrain boundary are potential candidates for genetic causes of congenital hydrocephaly. In this regard, a protein like Snf2l, which modulates chromatin structure and expression of En-1, may potentially have dire consequences for hydrocephaly (8). Although we are only beginning to unravel the multitude of factors that control the cell fate decisions in this region and the terminal differentiation of the specialized cells of the SCO and vel, it is apparent that there is extreme heterogeneity underlying hydrocephalus. It should also be mentioned that other transcription factors, such as Otx2, are known to be associated with hydrocephalus when inactivated in mice; however, such a phenotype is unlikely to be SCO-specific and likely constitutes a more general defect in brain development (62). Although development seems to have a significant role in the etiology of hydrocephalus, aberrant function of the SCO and vel cells has also been implicated in this disease.

Signal Transduction and the Regulation of SCO Secretion

The primary function of the SCO is to secrete high molecular weight glycoproteins that facilitate CSF flow and, in rodents, contribute to the formation of Reissner’s fiber (RF), which extends along the length of the CSF tract to the ampulla caudalis (89). The major secreted glycoprotein and constituent of RF is SCO-spondin, a highly conserved protein containing many protein segments that fostered its role in axonal pathfinding and neurite extension by monoaminergic neurons (99). Although the precise function of SCO-spondin has not been shown to be SCO-specific (80), it is possible that a terminal differentiation of SCO-spondin expression plays a role in CSF circulation and perhaps even in the regulation of calcium levels (86). The development and function of cilia (Pac1, R61) are critical in many tissues and may modulate the function of ciliary proteins (75). The PACAP receptor (PAC1) is a GPCR that can bind PACAP and modulate cell signaling (50, 106). The PACAP phospholipase C (PLC) interactions may inhibit a variety of pathways, including PKA and PLC/PIP2 interactions, and have been implicated in calcium signaling and modulation of cell function (98). Recent studies have shown that SCO agenesis is associated with defects in serotonin and dopaminergic neurons (50). The primary secretory granule (PSG) is a vitamin D3-type protein that is involved in the formation and maintenance of cilia (50). It is not yet known how SCO-spondin expression in the SCO domain is regulated, but it is possible that these pathways are involved in the regulation of SCO-spondin expression.

FIGURE 2. Molecular pathways in ependymal cells implicated in congenital hydrocephalus

Schematic representation of a SCO/vel ependymal cell highlighting the numerous molecular pathways underlying congenital hydrocephalus. Neurotransmitters (Pacap, serotonin) induce cell signaling pathways that alter target gene regulation, presumably genes encoding secreted glycoproteins and proteins involved in cilary function. The Socs7 protein is a regulator of the Jak/Stat signaling pathway. Ablation of several transcription factors (Msx1, Rfx3, Rfx4_v3) alters the terminal differentiation or cell fate of the ependymal cells. Numerous proteins (Mdnah5, Hydin, Pcdp1, Spag7, Polaris) and transcriptional regulators (Foxj1/En-4, Pol V) involved in the formation and function of cilia are implicated in hydrocephalus and are shown at the top of the diagram. The G-protein-coupled receptor (G-protein) is a regulator of the transport of cell adhesion molecules (Nmbc-IIb, cadherin) to the apical cell surface and presumably also for proper glycoprotein secretion.
Among the length underlying con-...sere high adhesion mol-...without a worsening of the disease.

Abnormal cytokine and growth factor signaling pathways have also been linked with hydrocephaly (reviewed in Ref. 112). One study has shown that sup-...growth factor signaling pathways have not yet been proven to be a primary cause of hydrocephalus; it represents an exciting area for future studies that would provide an additional layer of complexity to our understanding of the causal mechanisms of congenital hydrocephalus and SCO function.

The Contribution of Ventricular Cilia to CSF Homeostasis

The ventricular ependyma shares complementary functions with the SCO in regulating CSF homeostasis and preventing the onset of hydrocephalus (81). Besides the requirement for SCO glycoproteins and RF to prevent stenosis of the Sylvian aqueduct, a unidirectional laminar flow of CSF generated by the ciliated ependyma is essential (41).
Hydrocephalus in humans arises in several cil-iopathies, disorders that have been attributed to defects in cilia structure and function (4, 38, 40, 109). In the ventricular ependyma, the ciliary core, or axoneme, consists of an arrangement of a central pair of microtubules surrounded by nine peripheral microtubule doublets. Radial spokes project from the central pair and interact with the peripheral doublets, presumably to regulate interactions with dyneins, which are motor proteins that are responsible for generating ciliary beat (91).

Mouse axonemal dynein heavy chain (Mdnah5) was identified as a protein that is important for laminar CSF flow through the Sylvian aqueduct (41). Mdnah5-null mice have immotile cilia due to the absence of outer dynein arms in the axoneme (39). Its human counterpart, DNAH5, has been linked to outer dynein arm defects that lead to PCD, in the absence of outer dynein arms in the axoneme (105). Ependymal cells in these animals appear normal, suggesting a functional complement of cell adhesion molecules. Mutations in the vesicular transport protein Pac1 (Polc1/H9261) also develop hydrocephalus (47).

The molecular characterization of the hydrocephalus-3 (Hy3) mouse, a commonly studied model of hydrocephalus, resulted in the identification of the Hydin gene (22). Hydin is a putative microtubule binding protein (83) required for the formation of a specific projection emanating from one of the central pair microtubules [23, 53, 54]. Lechtreck et al. believe that Hydin is a dynein adaptor that is required to regulate the transition between the ciliary effective and recovery strokes [53, 54]. This proposal is consistent with observations that the epimembranous cilia of hy3 mice have difficulty bending, leading to ciliary beats with reduced frequency and impaired synchrony (53). At the same time, these cilia do not appear to have any structural defects other than the lack of this single central pair projection. The authors note that the phenotype is similar to that of PCD patients who suffer defects in the inner dynein arms or the radial spokes (21, 53).

Sperm-associated antigen 6 (Spag6) is another factor that associates with a specific central pair projection and, along with its interacting partners Spag16 and Spag17, is required for ciliary motility (83, 113–115). Like Hydin, Spag6 mutants suffer from hydrocephalus. The extent of the phenotype is made more severe when both Spag6 and Spag16 are knocked out, although Spag16–/– mice are not hydrocephalic (116). The ultrastructure of the epimembranous cells in these animals appears normal, suggesting a molecular pathology that is similar to hy3 mice. Moreover, Spag6 has been described as a candidate gene for hydrocephalus in H-Tx rats, another commonly studied hydrocephalus model (43).

PCD protein 1 (Pcdpl1) is another putative central pair-binding protein that, when ablated in mice, results in hydrocephalus (55). As with hy3 and Spag6–/– mice, the tracheal cilia of the Pcdpl1–/– mice have a reduced beat frequency but do not display any obvious ultrastructural axonemal defects. The ultrastructure and ciliary beat frequency of epimem-branous cilia were not reported, although Pcdpl1 was identified throughout the cilia of human brain epimembranous cells. In the Tg(37/106) mouse (57), mutations in the intrflagellar transport protein (91) Polaris/B18R also led to hydrocephalus. Although epimembranous cilia are shorter, disorganized, and beat asynchronously, the cause of hydrocephaly in these mice appears to be the regulation of intracellular and secretory mechanisms of the choroid plexus in response to the defects in the structure and function of its cilia (5, 6). IFT components appear to be well conserved and many await characterization, so it remains to be seen whether mutations in additional IFT factors also result in hydrocephalus.

Defects in the expression of transcriptional regulators that mediate cilogenesis can also lead to hydrocephalus. For example, Foxj1/Hfh-4 is an important transcriptional activator of numerous genes required for the development of motile cilia and has been associated with left-right asymmetry developmental defects and associated hydrocephaly (13, 20, 108). Similarly, mice that lack DNA polymerase λ (Pol λ) also develop hydrocephalus (47). Although Pol λ is generally considered to be a DNA repair enzyme, it is required for the proper expression of the axonemal inner dynein arms whose dysfunction likely contributes to the hydrocephaly in these animals (33).

In this section, we have highlighted recent advances characterizing defects in cilary structure and function that result in hydrocephalus. It is likely that additional proteins that interact with or comprise the cilia ultrastructure are potential candidates to be implicated in hydrocephalus in the near future.

**Cell Adhesion Molecules and Hydrocephalus**

The epimembranous cells of the SCO possess tight junctions and zonular adherens, which contribute to the formation of a blood-brain barrier between the circulation and the ventricular cavities (89). Adding to the complexity of its functions is accumulating evidence that the SCO is able to act as a mechanosensor, altering the way it secretes glycoproteins in response to signals sent from circulating blood, as shown in hypertensive rats (65). In this regard, it is intriguing that hypertension was also observed in both Pwc1-null and –/–expressing transgenic mice (50). Regardless, the presence of such a blood-brain barrier necessitates a functional complement of cell adhesion molecules.

Recent molecular evidence in humans indicates that the direction of cell adhesion molecules to the proper surface is vital. Mutations in the vesicular transport protein Snap-25 cause periventricular reduction in the choroid plexus and hydrocephalus (105). In human hydrocephalus and the hyh (hy3) mouse, the absence of a cell surface marker (a-Snap) which forms a meshwork of integrity in the choroid plexus and collects ventricular fluids (104). This phenotype is not seen in hyh mouse, replacing the ones that regulate SNAP-25.
transport proteins FILAMIN A and ARFGEF2 lead to periventricular heterotopia, which is associated with a reduction in cell adhesion and a loss of the neuroepithelium, and is sometimes accompanied by hydrocephalus (28, 77, 98). In the hydrocephalus with hop gait (hyh) mouse, hydrocephalus is accompanied by a denudation of the ependymal cell layer (14, 79, 105). Ependymal denudation of the SCO has been identified in cases of human hydrocephaly (25).

A mutation in the soluble NSF attachment protein α (α-Snap), which directs secretory vesicles to the apical surface of neurons, has been identified for the hyh phenotype (19, 36). α-Snap is known to direct cell adhesion molecules, such as E-cadherin and β-catenin, to the apical surface of neural progenitors (9, 19, 76). In vel cells, non-muscle myosin II-B heavy chain (Nmhc-IIb) forms a mesh-like structure with N-cadherin and β-catenin at the apical surface, thus it is possible that α-Snap is involved with the localization of one or more of these structural components (FIGURE 2) (61). Similar to the hyh phenotype, the loss of Nmhc-IIb results in a loss of integrity in the neuroepithelium, leading to hydrocephalus and defects in neuronal cell migration (61, 104). This phenotype can be somewhat rescued by replacing the expression of Nmhc-IIb with Nmhc-IIa (7).

Mouse-Human SCO Differences and the Relationship to the Human Condition

CNS patterning is a highly conserved process underpinned by fundamental molecular pathways and interactions in all vertebrates. Moreover, select classes of transcription factors such as the NRLH, homeobox, and paired box family are key regulators of CNS development in metazoans. Taken together, it suggests that mouse models represent a powerful system in which to understand the etiology of hydrocephaly in humans. Indeed, the presence of the SCO in vel appears to be a DNA sequence that is conserved across all vertebrates (47). During later embryonic stages and postnatally, the SCO begins to regress to the point where, by late childhood, secretion is limited to only a few remaining islets. Additionally, the glycoproteins secreted by the human SCO do not aggregate into RF nor do they immunoreact to antibodies raised against RF-glycoproteins in other mammals, indicative of some differences in the secretory role of the human SCO vs. that of the mouse (88). Indeed a pessimist would argue that these interspecies differences supersedes the benefits of studying hydrocephaly in models where the SCO is implicated. Although the species-specific roles of the SCO present challenges to the field, the adult vel still contributes to hydrocephalus in both species. In this regard, shared vel signaling pathways or factors involved in ciliary structure and function should allow for meaningful comparisons to be made; however, these comparisons are rare and tenuous at best. For example, the gene for the human PAC1 receptor is located at 7p15. Although a link could be made to communicating hydrocephalus, only a single patient with a duplication of this region has been described (69). The gene for its ligand, PACAP, is located at 18p11, and congenital hydrocephalus is one of the symptoms experienced by patients with tetrasomy 18p (102). Similarly, HYDIN, located at 16q22, is a candidate for one case of human hydrocephaly (16). A large-scale genetic screen has also recently revealed that mutations in a human-specific HYDIN paralog located at 1q21 may contribute to a number of behavioral and congenital brain disorders, although hydrocephalus was present in only a small number of these patients (15). Additional comparisons between human and mouse are summarized in a recent review of the genetics of human hydrocephaly (112).

Although we have highlighted a role for many factors in the etiology of hydrocephaly in the mouse, human studies identifying causative genes are lagging far behind. One reason for this delay may involve the natural genotype of hydrocephaly itself. It is a very heterogeneous disorder and without the availability of large families for genetic studies it is difficult to group patients together for successful linkage analyses. Another consideration is that many of the animal studies describe the ablation of specific genes that may be embryonic or early postnatal lethal in humans. Alternatively, variable mutations human genes should be studied in mice to further characterize the similarities and differences between the two species in disease development. In this regard, L1-CAM, an X-linked cell adhesion molecule important for neurite outgrowth, is the best characterized determinant of congenital human hydrocephaly, and mouse models have been shown to accurately recapitulate the human phenotype (44, 72, 90, 107). Overall, a combination of animal and human studies remains the best approach for disease gene identification.
Collectively, these studies demonstrate that defects in multiple aspects of SCO cell function are implicated in the development of congenital hydrocephalus. As such, the new front for SCO research is clearly toward a further understanding of the molecular mechanisms governing SCO development and function. The plethora of genetic mouse models available is phenomenal and should continue to be extremely valuable for researchers in this field and in the hunt for causes of human hydrocephalus.

Developmental studies will continue to elucidate the hierarchical transcription factor organization that dictates the stage-specific differentiation of these cells and underlies the critical points of functional regulation. Defining these pathways will present researchers with candidate disease genes and opportunities to augment differentiation of progenitors toward a SCO fate to generate cell culture models. Similarly, with a complete understanding of the signaling mechanisms between the CSF and SCO cell self-identifies ligands that could be administered to promote glycoprotein secretion and restore CSF homeostasis. Finally, the use of high throughput approaches will enhance the knowledge of the important protein-protein interaction. For example, proteomic approaches have been used in the initial characterization of the secreted glycoproteins from the SCO and, more generally, for delineating the cilary proteome (78). Interestingly, this proteomic study identified more than 600 proteins, of which over 200 were conserved between humans and Chlamydomonas, including a surprising number of proteins involved in signal transduction mechanisms (78). All of these approaches will increase our knowledge of SCO function and help elucidate where similarities to human hydrocephalus exist, thereby facilitating the characterization of genetic causes of congenital hydrocephalus.

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References


