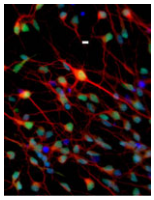
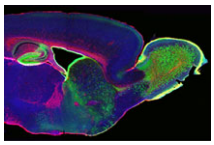


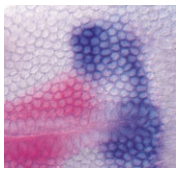
Stem cell neuronal differentiation in mice and men

The in vitro differentiation of mouse embryonic stem cells (mESCs) into forebrain neuronal types recapitulates many aspects of in vivo neural development. Directed in vitro differentiation of human embryonic stem cells (hESCs) into neuronal subtypes has been harder to achieve but, on p. 4053, Li and colleagues report that, in the absence of known morphogens, hESCs differentiate into dorsal telencephalic progenitors. They show that endogenous Wnt signalling drives this differentiation through the upregulation of truncated GLI3, a repressor of sonic hedgehog (SHH). High concentrations of SHH or inhibition of Wnt signalling, they report, almost completely convert the dorsal progenitors to ventral progenitors, in part by regulating the expression of active and repressive forms of GLI3. Finally, they show that these dorsal and ventral precursors differentiate into functional glutamatergic and GABAergic neurons, respectively. Interestingly, these results suggest that, although hESCs generate dorsal telencephalic cells in the absence of exogenous morphogens, whereas mESCs generate ventral precursors, a similar molecular mechanism controls dorsal-ventral telencephalic patterning in mice and humans.



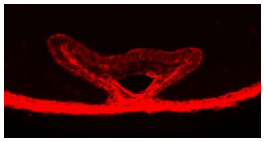
FoxJ1 sets scene for adult neurogenesis

Neurogenesis in adult mammals, which only occurs in limited brain regions, depends on a postnatal stem cell niche (SCN) along the lateral ventricles. One component of this SCN is an epithelial layer consisting of ependymal cells and a subset of astrocytes that differentiate from radial glia soon after birth. Jacquet and co-workers now report that the expression of the forkhead transcription factor FoxJ1 is required for this important differentiation event in mice (see p. 4021). They also show that a subset of FoxJ1$^+$ cells harvested from the SCN can self-renew and has neurogenic potential when cultured. Furthermore, they report that FoxJ1 regulates several genes that encode microtubule-associated proteins during early postnatal development and suggest that FoxJ1-dependent gene expression might control the transport of basal bodies to the surface of differentiating ependymal cells during the formation of the motile cilia that characterise these cells. Overall, these results provide new insights into how the adult SCN is established that could bring cell-based therapies for neural damage closer.



Networking to pattern the fly brain

During brain development in vertebrates and invertebrates, a sheet of neuroectodermal cells transforms into a complex three-dimensional structure that contains many neural cell types. The specification of these neural cells depends on the dorsoventral (DV) patterning of the neuroectoderm. Now, on p. 3937, Seibert and colleagues describe a novel regulatory network of homeobox transcription factors that underlies DV patterning in the developing *Drosophila* brain. Using expression studies and loss- and gain-of-function experiments, the researchers show that the *empty spiracles* gene (*ems*) and the *Nk6 homeobox* gene (*Nkx6*) encode key regulators of the DV genetic network. Intriguingly, *ems*, an anteroposterior patterning gene, controls the expression of the conserved homeobox DV genes *Nkx6*, *ventral nervous system defective* (*vnd*), *intermediate neuroblasts defective* (*ind*) and *muscle segment homeobox* (*msh*); conversely, these DV genes control the expression of *ems*. The researchers also show that cross-repressive interactions between pairs of homeodomain factors establish DV gene expression domains in the fly brain, a situation that resembles that seen in developing mouse brains.

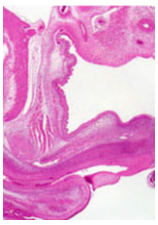


Shh, whisper it: external genitalia developing

External genitalia (the penis and the clitoris) develop from an embryonic primordium called the genital tubercle (GT), the development of which, like that of the limb bud, involves epithelial-mesenchymal interactions and the coordinated function of multiple signalling cascades. In this issue, three papers provide new information about the involvement of sonic hedgehog (Shh) in GT development in mice.

On p. 3959, Lin et al. describe the function of Shh during early GT development. By removing *Shh* at different stages of development, they show that Shh is required continuously during GT initiation and subsequent androgen-independent GT growth. By removing the Shh signal transducer smoothened in different tissue layers, they show that the GT mesenchyme is a target of Shh signalling. Finally, they show that Shh exerts its function in part by maintaining the GT signalling centre, the distal urethral epithelium (DUE), but also reveal that both DUE-dependent and -independent events occur downstream of Shh during GT development.

On p. 3969, Miyagawa et al. describe a novel signalling cascade that controls GT formation. By analysing *Gli* mutant mice, they show that the dosage of the Shh signal affects GT development and modulates the level of Wnt/β-catenin activity. This activity plays a key role in the formation of the GT by inducing multiple growth factors. However, note the researchers, both Fgf8 and Fgf4 are dispensable for GT outgrowth. Other data suggest that Wnt/β-catenin signalling in the DUE acts downstream of Shh signalling during GT outgrowth. Together, these data reveal conserved and divergent features of the developmental programmes that trigger GT and limb bud development.



Finally, Seifert et al. identify two temporal phases for Shh function during anogenital development (see p. 3949). Shh, they report, coordinates the outgrowth and patterning of the GT and the septation of the embryonic cloaca during the 'anogenital' phase. Then, during the 'external genital phase', Shh regulates only the development of the external genitalia. Other experiments show that Shh signals directly to the ectoderm to maintain a closed urethral tube, thus highlighting a new role for genital ectoderm in urethragenesis. Overall, these results provide insights into the causes of anogenital malformations, some of the most common human congenital abnormalities.

Jane Bradbury

IN JOURNAL OF CELL SCIENCE

Tβ4 shows some spine

The actin-binding peptide thymosin β4 (Tβ4) regulates cell shape by controlling intracellular actin availability and cell-adhesion molecule distribution; in neurons, for instance, Tβ4 regulates neurite outgrowth. It might also be neuroprotective, and in *J. Cell Sci.*, Daniela Merlo and colleagues now show that Tβ4 appears to control neural development and promote spinal-cord repair after injury. As Tβ4 is downregulated during neural differentiation, the authors decided to test the effect of decreasing Tβ4 levels in neural progenitor cells (NPCs). They find that in Tβ4-depleted NPCs, the adherens-junction components N-cadherin and β-catenin are upregulated, neurite outgrowth is enhanced and more neurons are generated. In a mouse model of spinal-cord injury, transplanting Tβ4-depleted NPCs improves the recovery of locomotion and triggers the increased expression of the adhesion molecule L1, thought to promote neuronal regeneration. Finally, axon regeneration and serotonergic fibre sprouting are enhanced around the NPC graft. The authors conclude that Tβ4 regulates neuronal differentiation, and highlight its therapeutic potential following spinal injury.

Mollinari C. et al. (2009). Downregulation of thymosin β4 in neural progenitor grafts promotes spinal cord regeneration. J. Cell Science 122, 4195-4207.