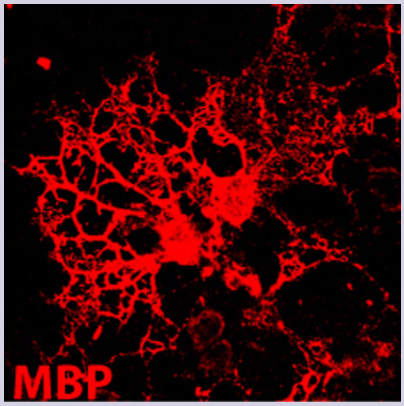

Myelin maintenance under microRNA control

Demyelinating disorders, or leukodystrophies, cause nervous system deficits owing to breakdown of the myelin sheath, which is essential for rapid and efficient neuronal communication. Prior studies of adult-onset autosomal dominant leukodystrophy (ADLD) have identified that the structural protein lamin B1 plays a role in maintaining myelin. Here, Shu-Ting Lin and Ying-Hui Fu further investigate the mechanisms by which expression of the lamin B1 gene, *LMNB1*, influences myelin integrity. They found that overexpressed lamin B1 halts the development of oligodendrocytes which form and maintain myelin in the central nervous system. They also identified a microRNA *miR-23*, which tightly regulates lamin B1 protein levels, as a potential therapeutic target in combating demyelinating disease.

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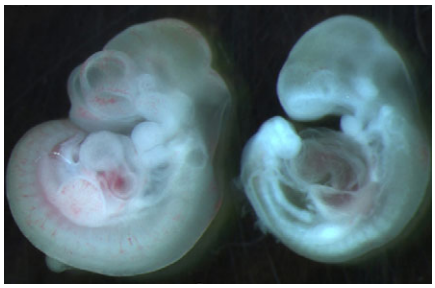
Endothelial cells key in cerebral angiogenesis



Cerebral cavernous malformations (CCM) induce recurring spells of cerebral hemorrhage and can cause focal neurological deficits and seizures. These malformations result from mutations in any of three known *CCM* genes. The role of CCM proteins in cerebral development and pathology is not well understood. Here, Gwénola Boulday and colleagues demonstrate the importance of *CCM* gene expression within endothelial cells (ECs) for proper vascular development. Deletion of *CCM2* in neuroglia precursor cells had no effect, but *CCM2* deletion in ECs severely impaired angiogenesis and vascular morphology, leading to embryonic death. This study highlights the complex function of CCM2 and the importance of studying ECs in CCM pathogenesis.

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Human stem cell-derived neurons model ALS

Amyotrophic lateral sclerosis (ALS) causes motor neuron degeneration characterized by progressive muscle weakness and eventual death. The translation of animal model work to human ALS studies has been largely unsuccessful owing to the complex biology of this disease. Saravanan Karumbayaram and colleagues expressed mutant forms of superoxide dismutase 1 (*SOD1*) linked to familial ALS in human embryonic stem cell-derived motor neurons. Neurons expressing mutant SOD1 exhibited abnormalities typical of ALS neurons, such as reduced life span and shorter cell processes. Using human-derived cells as shown here may more accurately model familial ALS, and in turn lead to more effective ALS therapies.

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Telomere dysfunction in cancer and skin disease

Xeroderma pigmentosum (XP) is an ultraviolet light-sensitivity syndrome caused by nucleotide excision repair (NER) defects, resulting in hyperpigmentation and an increased incidence of skin cancer. These symptoms also characterize the skin 'telopathies', which result from accelerated telomere shortening and exhaustion of the regenerative capacity of stem cells and lead to premature death. In this issue, Gerdine Stout and Maria Blasco investigate the pathways that connect stem cell dysfunction with telomere uncapping using a mouse model of telomere dysfunction which phenocopies the symptoms of XP patients. They demonstrate that both the absence of NER and the abrogation of p53 activity restore stem cell functionality. This work highlights the relationship between telomeres and stem cell renewal with the pathobiology of cancer.

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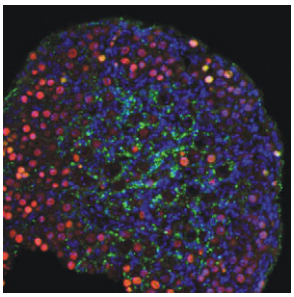
The connexin connection to fertility



Oculodentodigital dysplasia (ODDD) causes widespread abnormalities in the teeth, digits and eyes, as well as variable dysfunctional effects in the heart and brain. It is caused by a genetic mutation in connexin43 (Cx43), a gap junction protein widely expressed in the female reproductive system. Since the influence of Cx43 on fertility is unknown, Dan Tong and colleagues examined mice with a dominant loss-of-function mutation in Cx43 and characteristics of human ODDD. Compared with wild-type mice, mutant mice have similar numbers of germ cells but fewer pre-ovulatory follicles and no ovulation response to hormonal stimulation. Mutants also have less mating success and smaller litters. These data demonstrate a role for Cx43 in fertility and prompt further investigation of reproductive issues in ODDD patients.

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