COL4A1 mutations: new route to congenital muscular dystrophy

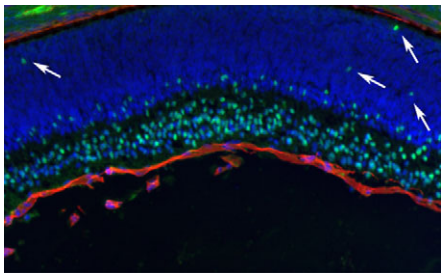

Image reproduced from Labelle-Dumais et al., 2011.

Muscle eye brain disease (MEB) and Walker Warburg syndrome (WWS) are among a spectrum of rare congenital muscular dystrophies (CMDs) that are inherited in an autosomal recessive pattern and are characterised by variable eye, brain and muscular defects. The cause of disease in a proportion of patients has been attributed to defects in the post-translational modification of dystroglycans, but Labelle-Dumais et al. now report a newly identified and distinct molecular defect that can also cause MEB and WWS. Their results show that mutations in the gene encoding basement membrane protein collagen IV α1 (COL4A1) are associated with these disorders in two patients, and that *Col4a1* heterozygous mice have defects resembling symptoms observed in humans with MEB and WWS. Molecular analyses support the previous hypothesis that *COL4A1* mutations cause toxic intracellular accumulation of the mutant protein, although further studies are required to rule out other pathomechanisms. These results provide evidence that *COL4A1* mutations can cause inherited CMD spectrum disorders in a dominant manner, and shed light on the role of this basement membrane protein in normal and disease physiology. *S.A.*

Labelle-Dumais, C., Dilworth, D. J., Harrington, E. P., de Leau, M., Lyons, D., Kabaeva, Z., Manzini, M. C., Dobyns, W. B., Walsh, C. A., Michele, D. E. et al. (2011). COL4A1 mutations cause ocular dysgenesis, neuronal localization defects, and myopathy in mice and Walker-Warburg syndrome in humans *PLoS Genet.* **7**, e1002062.

CFTR-F508 pigs provide new clues to cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease that greatly diminishes life span owing to impaired function of the lungs and intestinal epithelia. Although the F508 homozygous mutation in the anion channel protein cystic fibrosis transmembrane conductance regulator (CFTR) is commonly found in CF patients, the mechanisms by which this mutation causes disease are unclear. To investigate this issue in vivo, Ostedgaard et al. generated pigs homozygous for CFTR-F508. Unlike previously established mouse models of CF, CFTR-F508 pigs develop airway and intestinal disease that closely resembles human CF pathology. In vivo studies agreed with previous results carried out in cell culture systems, and showed that the F508 mutation causes CFTR misfolding and degradation, and the failure of the protein to localise at the apical surface of epithelial cells. CFTR-F508 pigs provide a relevant model to further investigate mechanisms of CF pathogenesis and for testing therapies that aim to increase CFTR activity. *M.R.*

Ostedgaard, L. S., Meyerholz, D. K., Chen, J. H., Pezzulo, A. A., Karp, P. H., Rokhlina, T., Ernst, S. E., Hanfland, R. A., Reznikov, L. R., Ludwig, P. S. et al. (2011). The ΔF508 mutation causes CFTR misprocessing and cystic fibrosis-like disease in pigs. *Sci. Transl. Med.* **3**, 74ra24.

Diseases of tissue stem cells: human iPSCs provide new clues

Dyskeratosis congenita (DKC) is caused by mutations in genes that control telomere homeostasis, and is characterised by clinical symptoms ranging from bone marrow failure to pulmonary fibrosis and cancer. Disease features vary with the affected gene, but are all thought to result from defects in the function of tissue stem cells. Although mouse models have provided some insight regarding underlying mechanisms, human studies are an essential component of research on DKC and will be required for developing new therapies. Batista et al. report that induced pluripotent stem cells (iPSCs) derived from fibroblasts of patients with DKC exhibit defects that mirror the biochemical features of the patients' cells, including impaired telomere homeostasis. The authors probed distinct pathological mechanisms underlying the disease using iPSCs derived from five patients carrying diverse mutations (in *TERT*, *TCAB1* and *DKC1*), and found that the extent of the defects observed in the iPSCs correlated with clinical disease severity. The findings suggest that restoring telomere homeostasis in tissue stem cells might be a promising therapy for DKC. They also support the application of iPSC-based systems to study other diseases caused by stem-cell defects. *S.A.*

Batista, L. F. Z., Pech, M. F., Zhong, F. L., Nguyen, H. N., Xie, K. T., Zaug, A. J., Crary, S. M., Choi, J., Sebastiano, V., Cherry. A. et al. (2011). Telomere shortening and loss of self-renewal in dyskeratosis congenita induced pluripotent stem cells. *Nature* [Epub ahead of print] doi:10.1038/nature10084.

Niemann Pick C disease: lessons from zebrafish development

Niemann Pick C disease is a rare, fatal lipid-storage disorder with no known cure. 95% of patients carry mutations in *NPC1* (Niemann-Pick disease, type C1), which encodes a protein involved in the intracellular trafficking of low-density lipoprotein (LDL)-derived cholesterol and plasma-derived glycolipids. Studies of mammalian models have shed light on pathological mechanisms caused by the mutation; now, Schwend et al. approach the issue from a developmental angle by identifying and studying the role of *npc1* in the zebrafish embryo. They find that *npc1* morphants display numerous abnormalities, including cholesterol mislocalisation, cell-movement defects and, at later stages of embryogenesis, cell death. Complementation of *npc1* morphants with mouse *Npc1* rescues the defect, indicating a high degree of gene homology between fish and mammals. Treatment of *npc1* morphants with steroids also rescues the defects, suggesting that reduced steroidogenesis is responsible for pathology caused by *npc1* loss of function. This study provides new clues for how to treat Niemann Pick C disease in humans, and suggests that the zebrafish embryo is a valid model to screen for novel therapies. *M.R.*

Schwend, T., Loucks, E. J., Snyder, D. and Ahlgren, S. C. (2011). Requirement of Npc1 and availability of cholesterol for early embryonic cell movements in zebrafish. *J. Lipid Res.* [Epub ahead of print] doi: 10.1194/jlr.M012377.

Written by editorial staff. © 2011. Published by The Company of Biologists Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial Share Alike License (http://creativecommons.org/licenses/by-nc-sa/3.0), which permits unrestricted non-commercial use, distribution and reproduction in any medium provided that the original work is properly cited and all further distributions of the work or adaptation are subject to the same Creative Commons License terms.