Tissue regeneration in mammals: clues from *Acomys* mice

Image reproduced from Seifert et al. (2012) with permission.

Compared with most vertebrate species, adult mammals are considered to have very limited regenerative capacity. Now, a report by Seifert et al. on two species of African spiny mice (*Acomys*) suggests that regeneration of certain tissues does occur in some mammals. *Acomys* skin tears with handling and, in the wild, can be shed in large amounts to escape predators. The authors found that *Acomys* species have skin that is 20-times weaker than the *Mus* species conventionally used in the lab. *Acomys* showed rapid healing of skin wounds and little evidence of scarring, whereas *Mus* deposited large amounts of extracellular matrix that contributed to fibrosis. In addition, unlike *Mus*, *Acomys* species contained regenerating hair follicles in newly healed wounds. *Acomys* species also showed rapid closing of 4-mm punch wounds in ear tissue, which involved regeneration of skin, hair follicles, sebaceous glands, adipose cells and cartilage (but not muscle). In contrast, *Mus* were incapable of closing ear punch wounds and formed a scar composed of cartilage. Finally, the authors show that tissue regeneration in *Acomys* might occur through formation of a structure resembling a blastema, a mass of lineage-restricted progenitor cells that has been characterised in amphibians that can re-grow limbs. These results highlight the value of studying diverse model organisms and open up new opportunities for studying regeneration in mammals.

Seifert, A. W., Kiama, S. G., Seifert, M. G., Goheen, J. R., Palmer, T. M. and Maden, M. (2012). Skin shedding and tissue regeneration in African spiny mice (*Acomys*). *Nature* **489**, 561-565.

CF-related diabetes: new insights from ferrets

Individuals with cystic fibrosis (CF) frequently also suffer from diabetes, which worsens CF prognosis. CF is caused by mutation of the CFTR chloride channel, leading to dysfunction of several internal organs, including the pancreas. Recently, engineered ferret and pig models of CF have been developed that more closely recapitulate the disease than rodent models used previously. Olivier et al. now report on the early stages of pancreatic pathology and diabetes development in CF ferrets, which are more similar to humans than are pigs with respect to the progression of pancreatic disease after birth. The authors found early signs of abnormal insulin secretion and glucose tolerance in neonatal CF ferrets, before overt histopathological changes occurred in the pancreas. Pancreas pathology that was associated with inflammation and fibrosis progressed in the first month of life, with an age-dependent rise in blood glucose. Compared with non-CF ferrets, newborn CF ferrets had fewer large islets and, in vitro, islets from newborn CF ferrets showed abnormal glucose-responsive insulin secretion, despite high insulin content. These results suggest an intrinsic defect in islets of CF ferrets that is present at birth. Further studies could help to develop strategies for treatment or prevention of CF-related diabetes in humans.

Olivier, A. K., Yi, Y., Sun, X., Sui, H., Liang, B., Hu, S., Xie, W., Fisher, J. T., Keiser, N. W., Lei, D. et al. (2012). Abnormal endocrine pancreas function at birth in cystic fibrosis ferrets. *J. Clin. Invest.* **122**, 3755-3768.

Immune system eliminates polyploid cancer cells

Polyploid cells – those with more than two sets of chromosomes – are normally eliminated by cell-autonomous mechanisms; when this mechanism fails, cancer can develop. Senovilla et al. now report that there is an additional, non-cell-autonomous mechanism that eliminates polyploid cells. They found that cells with four or more sets of chromosomes have increased levels of endoplasmic reticulum stress, which leads to cell-surface exposure of calreticulin (CRT). The authors went on to show that CRT cell-surface exposure stimulates immunosurveillance: when injected into immunocompetent (but not immunodeficient) mice, hyperploid CT26 colon cancer cells induced cancer more readily than euploid CT26 cells. This effect was not observed if CRT was depleted from hyperploid cells before injection. CRT was found to be important for T-cell-mediated immunoselection against polyploid cells in the adoptive transfer experiments, as well as in chemically or genetically induced cancer in mice. Finally, the authors show that breast cancer patients who responded well to therapy had residual carcinoma cells with smaller nuclei, and showed a greater local immune response, compared with nonresponders. These results shed light on a previously unappreciated cancer immunosurveillance mechanism.

Senovilla, L., Vitale, I., Martins, I., Tailler, M., Pailleret, C., Michaud, M., Galluzzi, L., Adjemian, S., Kepp, O., Niso-Santano, M. et al. (2012). An immunosurveillance mechanism controls cancer cell ploidy. *Science* **337**, 1678-1684.

Niemann-Pick disease and platelet dysfunction

Niemann-Pick type C (NPC) diseases, caused by mutations in *NPC1* or *NPC2*, are rare inherited disorders affecting cholesterol metabolism, and are characterised by progressive neurodegeneration and premature death. In some affected individuals, haematological defects such as thrombocytopenia (low platelet counts) and anaemia are also observed. Louwette et al. now characterise platelet abnormalities in three unrelated patients carrying *NPC1* mutations, and in NPC1-depleted zebrafish embryos. In patients, platelets were present in normal numbers but showed functional impairments. Patients' haematopoietic stem cells were defective in differentiation into megakaryocytes (platelet precursors), although red blood cells differentiated normally. Zebrafish embryos depleted for NPC1 showed abnormal numbers of thrombocytes and red blood cells, suggesting that the entire myeloid lineage was affected. How defects in lipid metabolism caused by NPC1 mutations lead to defects specifically in the myeloid lineage remains an open question.

Louwette, S., Régal, L., Wittevrongel, C., Thys, C., Vandeweeghde, G., Decuyper, E., Leemans, P., De Vos, R., Van Geet, C., Jaeken, J. et al. (2012). NPC1 defect results in abnormal platelet formation and function: studies in Niemann-Pick disease type C1 patients and zebrafish. *Hum. Mol. Genet.* [Epub ahead of print] doi: 10.1093/hmg/dds401.