Stress tolerance influences diabetes risk

Type 2 diabetes mellitus (T2DM) is one of many disorders where genetic variation determines disease susceptibility. As gene variation is linked to native environment and social behavior, studies on lab animals are limited by artificial influences on diet and breeding. Thus, Roxanne Oriel and colleagues examined T2DM in two genetically similar species of field mice (Peromyscus) that differ in native environment and behavior. They show that males of one species have both low stress hormone levels and stress-induced blood sugar increases not seen in a notably calmer species, or in females. In addition to tests using consomic mice, their data suggests that stress-induced blood sugar elevation is the result of Y-chromosome-linked genetic variance. Their work demonstrates the importance of behavior and environmental background in studying genetic variation and diabetes risk.

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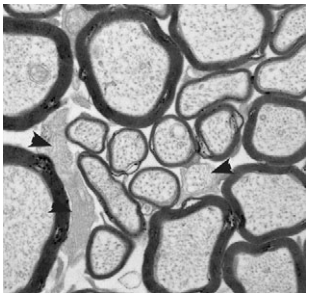
Enzyme excess leads to myelin degeneration



Myelin, the axon insulator needed for effective action potential propagation, breaks down in several neurological diseases, most notably multiple sclerosis (MS). Patients afflicted with MS suffer progressive deficits in balance, coordination and movement, as well as visual and sensory disturbances. Here, Abdiwahab Musse and colleagues report on a mouse model of demyelinating disease created through overexpression of peptidylarginine deiminase 2 (PAD2), an enzyme which converts peptide-bound arginine, a positively charged amino acid, into citrulline, a neutral amino acid, in myelin basic protein. The PAD2-overexpressing mice had white matter lesions as well as nude and hypomyelinated axons. Behavioral analysis showed that, like MS patients, the mice also had abnormal movement, balance and coordination. The authors' work presented here highlights the importance of PAD2 regulation in myelin stability, and presents a new animal model for demyelinating disease.

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Improving dialysis by disrupting cell change

Patients using peritoneal dialysis (PD) to treat end-stage renal failure must often discontinue treatment owing to an eventual loss of peritoneal filtration ability. This loss is preceded by peritoneal cell changes reminiscent of epithelial-to-mesenchymal transition (EMT), which in turn lead to inflammation and fibrosis of the peritoneum. Although EMT is a normal process during development, it has also been observed and studied in tumorigenesis and chronic inflammation. Here, Raffaele Strippoli and colleagues show that an ERK/NF-κB/Snail1 signaling cascade triggers EMT in peritoneal mesothelial cells. ERK and NF-κB inhibition can prevent and reverse this transformation in mesothelial cells collected from PD patients, suggesting that this pathway can be a therapeutic target for maintaining the efficacy of PD.

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Putting a HE(S)X on hypopituitarism

Mutations in the homeobox gene *HESX1* contribute to a variety of pituitary-linked diseases in humans, resulting in a wide array of clinical manifestations. Here, Ezat Sajedi and colleagues show that the murine homologue of *HESX1* is necessary for normal pituitary development and function, and has subtle effects on eye precursor cells and in the anterior brain. In addition, expression of the two *HESX1* mutations associated with human disease, resulted in distinct murine phenotypes. The differential consequence of *HESX1* expression in different tissue types and the unique manifestations of its mutations provide insight into the complex variability found in human hypopituitarism.

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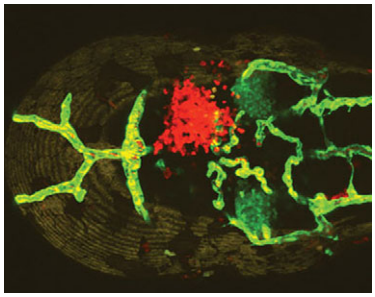
Genetic contributions to stroke



Severe stroke, resulting from intracranial hemorrhage (ICH), is often associated with mutations in a small subset of genes, called *CCM* (cerebral cavernous malformation) genes. However, the variable clinical effects of *CCM* gene mutations are not understood. Aniket Gore and colleagues altered the expression of various *CCM* genes, or their effectors, in zebrafish embryos to study the genetic basis of susceptibility. Although reduced expression of individual CCM pathway proteins has little phenotypic effect, combinations of otherwise silent deficits disrupt endothelial junctions and result in a high incidence of ICH. Thus, small, individually silent defects in the CCM pathway strongly synergize to increase susceptibility to ICH.

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