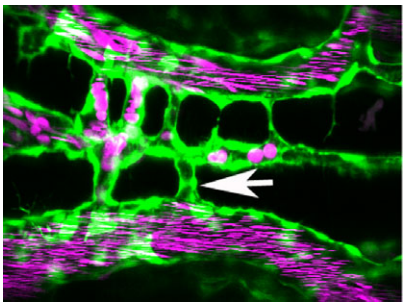
alk1 mutant zebrafish shed light on the etiology of AVMs



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Arteriovenous malformations (AVMs) are abnormal and direct connections between arteries and veins, causing disorganised blood flow and weak vessel structure. Although nosebleeds are a common clinical outcome of AVMs, more serious hemorrhages in the brain and lungs can occur. Corti et al. studied AVMs in zebrafish embryos carrying a mutant version of *activin receptor-like kinase 1* (*alk1*), which is associated with hemorrhagic telangiectasia type 2 (HTT2), a vascular disorder characterised by AVMs. In the absence of functional Alk1, initial increases in endothelial cell number cause arteries nearest to the embryonic heart to become enlarged, increasing blood flow to downstream vessels, which then compensate by stabilising normally transient arteriovenous connections, consequently generating AVMs. The authors also found that *alk1* expression requires blood flow, suggesting that the protein functions as a sensor of shear stress to limit vessel size. These results provide insight into the etiology of HTT2-associated AVMs and open up new avenues for therapeutic intervention. *M.R.*

Corti, P., Young, S., Chen, C. Y., Patrick, M. J., Rochon, E. R., Pekkan, K. and Roman, B. L. (2011). Interaction between *alk1* and blood flow in the development of arteriovenous malformations. *Development* **138**, 1573-1582.

Mutant huntingtin in the hypothalamus causes metabolic dysfunction

Huntington's disease (HD) is a neurodegenerative disorder that is clinically diagnosed by overt motor dysfunction, but metabolic defects such as insulin resistance and increased appetite often occur years before diagnosis. Triplet repeat expansion in the huntingtin gene (*htt*) is the primary cause of neuropathology but, because it is ubiquitously expressed, it has been hypothesised that mutant *htt* might also affect other tissues. Hult et al. now show that expression of mutant *htt* in the hypothalamus – a brain region central to regulating metabolism – causes metabolic abnormalities. Mice expressing a fragment of mutant *htt* selectively in the hypothalamus became obese, and developed insulin and leptin resistance. Furthermore, the development of metabolic abnormalities in transgenic mice expressing mutant *htt* ubiquitously could be prevented by hypothalamus-specific deletion of the gene in young mice. These findings establish a causal link between mutant *htt* in the hypothalamus and metabolic dysfunction, and suggest that metabolic readouts will be useful in assessing HD therapy involving silencing of *htt* in brain. *S.A.*

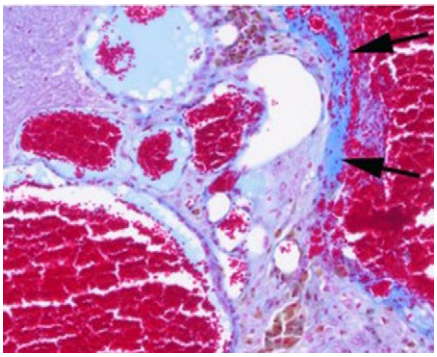
Hult, S., Soylu, R., Björklund, T., Belgardt, B. F., Mauer, J., Brüning, J. C., Kirik, D. and Petersén, Å. (2011). Mutant huntingtin causes metabolic imbalance by disruption of hypothalamic neurocircuits. *Cell Metab.* **13**, 428-439.

C. elegans screen for modulators of fat storage

Metabolic disorders such as obesity and type 2 diabetes are challenging to treat owing to the complex regulatory mechanisms that maintain energy balance. Efforts to identify drugs that target fat accumulation have found many compounds that show high efficacy in cell culture systems but have limited success when tested in whole animals. Lemieux et al. now report a new in vivo strategy using *C. elegans*, and screened 3200 small molecules to find regulators of fat storage. They discovered several compounds that either increased or decreased fat content without affecting feeding, growth or reproduction. A subset of these compounds was also found to regulate fat storage in mammalian and insect cell lines. Notably, one compound reduced fat accumulation via a transcription factor with no previously described role in metabolism. These data demonstrate a cost-effective and high-throughput in vivo screen for small molecules that regulate fat storage, with advantages over existing cell-based assays. *M.R.*

Lemieux, G. A., Liu, J., Mayer, N., Bainton, R. J., Ashrafi, K. and Werb, Z. (2011). A whole-organism screen identifies new regulators of fat storage. *Nat. Chem. Biol.* **7**, 206-213.

Two distinct routes to CCM pathology



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Vascular malformations in the brain known as cerebral cavernous malformations (CCMs) are a cause of seizures and hemorrhagic stroke. Familial cases of CCM are caused by mutations in one of three genes – *KRIT1*, *CCM2* or *PDCD10* – and it has been hypothesised that the proteins they encode form a complex. However, Chan et al. now report that the molecular pathways perturbed by mutations in the different genes are distinct, despite causing similar clinical pathology. The authors used inducible, tissue-specific mouse models of CCM to show that loss of *Pdcd10* has different effects on vascular development and endothelial signalling pathways than loss of *Krit1* or *Ccm2*. Despite these differences, they found that loss of heterozygosity is the common genetic mechanism causing CCMs with both molecular phenotypes. These findings indicate that CCMs with similar pathology can be caused by multiple mechanisms, and that treatment strategies should take into account the causative mutation. *S.A.*

Chan, A. C., Drakos, S. G., Ruiz, O. E., Smith, A. C. H., Gibson, C. C., Ling, J., Passi, S. F., Stratman, A. N., Sacharidou, A., Revelo, M. P. et al. (2011). Mutations in 2 distinct genetic pathways result in cerebral cavernous malformations in mice. *J. Clin. Invest.* [Epub ahead of print] doi:10.1172/JCI44393.