Vascular disease: a novel molecular method for blood vessel formation

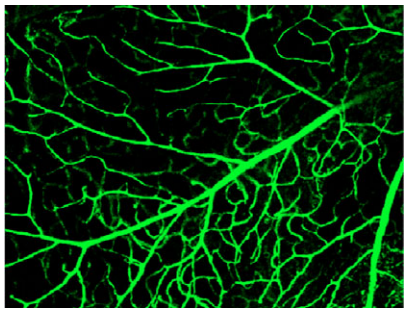


Image reproduced from Walshe et al. (2009). *PLoS One* **4**, e5149.

For patients with advanced vascular disease, improving the efficacy of arteriogenesis may provide an alternative to invasive bypass surgery. Ren et al. discovered that shifting the balance between extracellular signal-regulated kinase (ERK)1/2 and phosphoinositide 3-kinase (PI3K)-Akt1, two crucial signaling arms that are activated by VEGF, stimulates arterial growth in mouse and zebrafish models of vascular disease. ERK1/2 is highly activated in growing arteries. This is in contrast to the PI3K-Akt1 pathway, which is thought to have an arterial stabilizing effect. In mice and zebrafish with decreased VEGF responsiveness and ERK1/2 activity, researchers restored ERK1/2 activation by downregulating PI3K-Akt1 activity or by introducing a constitutively activating ERK1/2. Both approaches stimulate arterial development. Inhibiting the PI3K-Akt1 pathway in an atherosclerotic mouse model effectively stimulated arterial formation. Thus, the PI3K-Akt1 pathway is a potential drug target for vascular disease. *M.R.*

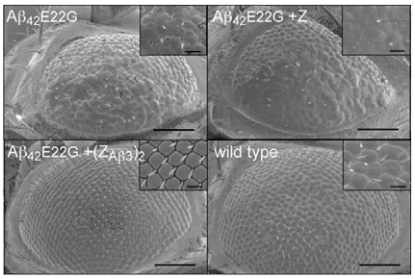
Ren, B., Deng, Y., Mukhopadhyay, A., Lanahan, A. A., Zhuang, Z. W., Moodie, K. L., Mulligan-Kehoe, M. J., Byzova, T. V., Peterson, R. T. and Simons, M. (2010). ERK1/2-Akt1 crosstalk regulates arteriogenesis in mice and zebrafish. *J. Clin. Invest.* Mar 8 [Epub ahead of print] [doi:10.1172/JCI39837].

Cancer: the two faces of Dicer

Apoptosis is a highly coordinated, multistep process that is often deregulated in diseases such as cancer and autoimmune disorders. It is associated with chromosomal fragmentation by deoxyribonucleases (DNases). Although many DNases have been characterized, Nakagawa et al. have discovered that Dicer, a highly conserved ribonuclease (RNase) that is known to produce small gene-silencing RNAs, also functions in chromosomal fragmentation. Researchers demonstrated that *Dicer* (*dcr-1*) gene inactivation in *C. elegans* blocks chromosomal fragmentation. The apoptosis executioner enzyme CED-3 caspase cleaves DCR-1 to generate a DCR-1 fragment with DNase activity that destroys its RNase function. Overexpression of the DCR1 DNase fragment induces DNA fragmentation. This discovery shows the conversion potential of an RNase to a DNase, and elucidates an important regulatory mechanism in apoptosis, which is relevant to many human diseases. *M.R.*

Nakagawa, A., Shi, Y., Kage-Nakadai, E., Mitani, S. and Xue, D. (2010). Caspase-dependent conversion of Dicer ribonuclease into a death-promoting deoxyribonuclease. *Science* Mar 11 [Epub ahead of print] [doi:10.1126/science.1182374].

Neurodegeneration: Aβ peptide clearance in Alzheimer's disease



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Alzheimer's disease (AD) is the most common form of dementia. This incurable and progressive disease is closely associated with extracellular amyloid beta (Aβ) peptides that aggregate to form plaques and neurofibrillary tangles in the gray matter of the brain. Plaques and tangles are important for the neuropathological verification of AD, but their role in disease pathogenesis is unclear. Luheshi, Hoyer et al. evaluated a small stable protein called Zaβ3 that specifically binds to Aβ peptides with high affinity. When expressed in the brain of Drosophila models of AD, Zaβ3 sequesters Aβ peptide and inhibits its aggregation and toxicity. AD flies expressing Zaβ3 lived longer than AD controls and retained significantly less Aβ peptide, suggesting that enhanced clearance of the protein reduces disease pathology. This fly model demonstrates a direct role for Aβ plaque formation in neurodegeneration. Since small molecule binding to Aβ peptide reduces its aggregation and toxicity, and extends survival, there could be potential for drugs that promote Aβ peptide clearance in AD patients. *K.K.*

Luheshi, L. M., Hoyer, W., de Barros, T. P., van Dijk Härd, I., Brorsson, A. C., Macao, B., Persson, C., Crowther, D. C., Lomas, D. A., Ståhl, S. et al. (2010). Sequestration of the Aβ peptide prevents toxicity and promotes degradation in vivo. *PLoS Biol.* **8**, e1000334.

Regeneration: the Hydra genome revealed

Hydra are freshwater cnidarians with a tubular body and mobile tentacles: a superficial appearance that is very distinct from humans. However, they are of important biological interest because of their ability to regenerate and because they are one of the few animals that apparently escape some characteristic effects of aging. Hydra also contain homologues to human Myc and Max, which influence cancer and stem cell biology. Chapman, Kirkness, Simakov et al. reveal that the genomic sequence of *Hydra magnipapillata* contains an estimated 20,000 protein-coding genes, surprisingly similar to the number of protein-coding genes estimated in the human genome. Some important genes are conserved from Hydra to humans, including molecules involved in neuronal signaling. There is significant conservation of cell-cell contact proteins, such as cadherins and β-catenin. The conservation of some systems from Hydra to humans suggests that the Hydra may be a simple and valuable model for medically relevant research. *K.K.*

Chapman, J. A., Kirkness, E. F., Simakov, O., Hampson, S. E., Mitros, T., Weinmaier, T., Rattei, T., Balasubramanian, P. G., Borman, J., Busam, D. et al. (2010). The dynamic genome of Hydra. *Nature* **464**, 592-596.