Metabolism and aging: ER stress prolongs life

Metabolism is linked to both stress responses and longevity. Environmental stress decreases the cellular response to signaling from insulin or the similar hormone insulin-like growth factor 1 (IGF-1). It is thought that insulin or IGF-1 resistance protects cells from potential damage, but the mechanisms that confer this physiological advantage are largely unknown. Henis-Korenblit et al. show that stress originating from the accumulation of unfolded proteins in the endoplasmic reticulum (ER) leads to the expression of longevity genes in *C elegans*. Gene expression is activated through ER-specific stress response proteins that collaborate with molecules that are important regulators of insulin signals, such as DAF-16, and the cell cycle, such as FOXO. This response alleviates the accumulation of unfolded proteins but also more globally influences aging. The coordination of these responses suggests that intervention along these pathways might help treat a variety of human diseases associated with ER dysfunction. *K.K.*

Henis-Korenblit, S., Zhang, P., Hansen, M., McCormick, M., Lee, S. J., Cary, M. and Kenyon, C. (2010). Insulin/IGF-1 signaling mutants reprogram ER stress response regulators to promote longevity. *Proc. Natl. Acad. Sci. USA* May 11 [Epub ahead of print] [doi: 10.1073/pnas.1002575107].

Neurodegeneration: Alzheimer's disease

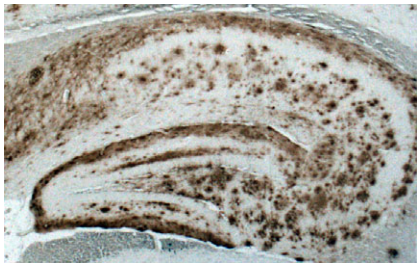

Image reproduced from Hemming et al. (2007). *PLoS Med.* **4**, e262.

A hallmark of Alzheimer's disease (AD) is the accumulation of amyloid beta (Aβ) peptide into plaques in the brain. The role of these plaques in the pathophysiology of disease is unclear, but some treatments that disrupt plaque formation are effective. Secretase inhibitors can disrupt plaque formation but they have toxic side-effects that are ameliorated by intermittent therapy regimens. However, there is concern that Aβ might rapidly accumulate when the inhibitor is withdrawn. Cook et al. determined that the γ-secretase inhibitor (GSI) MK-0752 inhibits Aβ accumulation in rhesus monkeys without an elevation in CNS Aβ accumulation after drug withdrawal. By administering stable isotopes concomitantly with the GSI, they determined that only plasma levels of Aβ rebounded after treatment, whereas CNS levels remained low. During secretase inhibition, an alternate pathway in the CNS metabolized Aβ precursors. This suggests that it may be safe to treat AD transiently with secretase inhibitors. *K.K.*

Cook, J. J., Wildsmith, K. R., Gilberto, D. B., Holahan, M. A., Kinney, G. G., Mathers, P. D., Michener, M. S., Price, E. A., Shearman, M. S., Simon, A. J. et al. (2010). Acute gamma-secretase inhibition of nonhuman primate CNS shifts amyloid precursor protein (APP) metabolism from amyloid-beta production to alternative APP fragments without amyloid-beta rebound. *J. Neurosci.* **30**, 6743-6750.

Mental health: spadin, a fast-acting antidepressant

Depression is the most commonly diagnosed mental illness, yet antidepressants are either effective only after prolonged treatment or remain largely ineffective. Mazella et al. identified a naturally occurring peptide, spadin, as a fast-acting antidepressant that interacts with, and blocks the activity of, a mood-regulating potassium channel, TREK-1. Mice lacking TREK-1 are resistant to depression and exhibit behavior similar to mice treated with antidepressants. Spadin-treated mice displayed a similar resistance to depression as TREK-1-deficient mice within only four days, as opposed to the several weeks necessary to respond to conventional therapies. Short-term spadin treatment induced classical antidepressant markers including increased CREB expression and neurogenesis. Unlike current depression medication, spadin's rapid onset of action makes it a strong candidate to develop novel and more successful antidepressant medication. *M.R.*

Mazella, J., Pétrault, O., Lucas, G., Deval, E., Béraud-Dufour, S., Gandin, C., El-Yacoubi, M., Widmann, C., Guyon, A., Chevet, E. et al. (2010). Spadin, a sortilin-derived peptide, targeting rodent TREK-1 channels: a new concept in the antidepressant drug design. *PLoS Biol.* **8**, e1000355.

Angiogenesis: coupling ephrin-B2 and VEGF

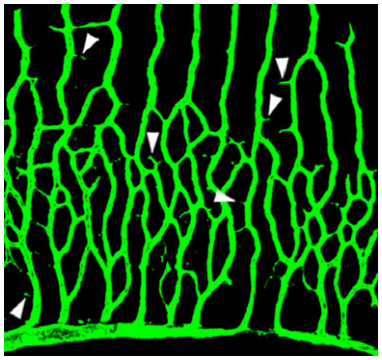

Image reproduced from Cao et al. (2008). *PLoS ONE* **3**, e2748.

Angiogenesis is highly coordinated to expand and remodel blood vessels. Vascular endothelial growth factors (VEGF) are potent angiogenic stimuli; however, little is known about how endothelial cells (ECs) receive and respond to cues that promote blood vessel sprouting. Wang et al. discovered that ephrin-B2, a transmembrane ligand for Eph receptor tyrosine kinases, promotes angiogenic EC proliferation, motility and sprouting. Genetic knockdown of ephrin-B2 in both mice and zebrafish reduced angiogenesis and decreased EC number and vessel branching. EC-specific ephrin-B2 overexpression induced vessel sprouting and lengthened vessel protrusions into the extracellular matrix. Ephrin-B2 regulates VEGF receptor internalization and signaling activity that is necessary for EC proliferation and motility. *M.R.*

Wang, Y., Nakayama, M., Pitulescu, M. E., Schmidt, T. S., Bochenek, M. L., Sakakibara, A., Adams, S., Davy, A., Deutsch, U., Lüthi, U. et al. (2010). Ephrin-B2 controls VEGF-induced angiogenesis and lymphangiogenesis. *Nature* May 5 [Epub ahead of print] [doi:10.1038/nature09002].