**Insulin breaks hearts**

Insulin signaling, which is required to keep blood sugar levels steady, may be deleterious for heart cells as they age, according to Robert Wessells, Rolf Bodmer (The Burnham Institute, La Jolla, CA), and colleagues. When insulin signaling is compromised, however, the old flies remain young at heart.

Animals with less insulin live longer, but the relevant effects on individual organs had not been assessed. The new results show that insulin is deleterious to fly heart function. As flies age, their hearts beat more slowly and are more prone to failure under stress. But this deterioration was delayed in mutant flies that did not perceive as much insulin.

Insulin’s effects on the heart are not mediated by systemic actions downstream of insulin. Heart-specific reduction in insulin signaling also improved heart performance in elderly flies. Activation of cardiac insulin signaling, in contrast, made young flies more prone to stress-induced heart failure.

Heart-specific improvements did not extend the fly’s lifespan, but heart activity is much more critical to mammalian survival. If the effects of insulin and insulin-like growth factors are similar in humans, Bodmer dreams of “organ-specific interventions to improve the quality of old age.”

Reference: Wessells, R.J., et al. 2004. Nat. Genet. 36:1275–1281.

**Time keepers abound**

Every cell in the body has its own little clock, according to Emi Nagoshi, Ueli Schibler (University of Geneva, Switzerland), and colleagues. These peripheral clocks may be closely related to the body’s central clock—the suprachiasmatic nucleus (SCN).

Neurons of the SCN maintain circadian gene expression for long periods of time. Other cells, however, were thought to rely on the SCN to maintain their oscillations, as the amplitude of gene expression oscillations in fibroblast cultures lessens rapidly with time in culture. But Schibler’s group shows that the examination of mass cultures masks the continued ability of each cell to maintain strong oscillations.

By looking at individual fibroblasts, the authors were able to see persistent oscillations. Even after mitosis, daughter cells continued the rhythm of the mother, although with a slight phase shift, probably due to the transient suspension of transcription. Mitosis itself is also gated by the oscillations, although the cellular advantage to this gating is unclear.

Mathematical modeling suggested that global culture oscillations are diluted over time by slight differences in the periodicities of each cell’s clock. Resynchronization was achieved in cultured cells by activation of a wide variety of signaling pathways, which reset all cells to a common point. In animals, peripheral clocks are synchronized by feeding cycles, which depend on sleep–wake cycles. As the SCN controls sleep cycles, it automatically synchronizes the oscillations in peripheral cell types.

Reference: Nagoshi, E., et al. 2004. Cell. 119:693–705.

**Checking in on spindle size**

Only replicated chromosomes should journey down mitotic spindles. The premature segregation of unreplicated DNA is prevented by the replication checkpoint, which is widely believed to block entry into mitosis when replication forks are stalled. But Vaidehi Krishnan, Uttam Surana, and colleagues (Institute of Molecular and Cell Biology, Singapore) show that the checkpoint has a more direct target—it prevents spindle elongation.

During replication stalls, budding yeast cells build short mitotic spindles. These spindles elongate in replication checkpoint-defective rad53 or mec1 mutants, thus causing untimely and uneven distribution of the DNA. Surana’s group shows that this elongation occurs in the absence of most of the hallmarks of mitosis, including APC activation, cohesin cleavage, and biorientation.

“At least in early S phase, when cohesion and biorientation have not been established, cells are not looking ahead [to mitosis],” says Surana. “They are just solving a local problem of preserving nuclear integrity by preventing spindle elongation.” Rad53 and Mec1 kinases accomplish this by down-regulating the microtubule-binding proteins Cin8 and Stu2, which elongate spindles. The microtubule destabilizing motor Kip3 also helped by restricting spindle elongation during synthesis delays.

Cin8 overexpression forced premature nuclear division in checkpoint-competent cells. Conversely, overexpression of Rad53 in cells whose DNA replicated normally resulted in abnormal and fragmented spindles.

Reference: Krishnan, V., et al. 2004. Mol. Cell. 16:687–700.