Learning after sleep loss

Sleep deprivation causes extensive biological effects, including insulin resistance, risk of obesity and cognitive defects. Following sleep loss, organisms exhibit sleep homeostasis (an increase in sleep) that is thought to restore biological functions. Neither the biological functions restored during sleep homeostasis nor the genes that regulate sleep homeostasis are known. Now, Paul J. Shaw and colleagues show that *Lsd2* (encoding Lipid storage droplet 2) mutant flies do not display sleep homeostasis following sleep deprivation induced by starvation (*PLoS Biol.* 8, e1000466, 2010). To determine whether loss of *Lsd2* leads to a global physiological impairment of many processes including sleep homeostasis or whether it specifically protects against the negative effects of sleep loss, the authors tested whether *Lsd2* mutants displayed learning impairment following sleep deprivation. *Lsd2* mutants showed normal levels of learning after 12 hours of sleep loss, suggesting that lipid metabolism is involved in regulating sleep homeostasis. Previous studies have shown that sleep loss can activate metabolic genes. The findings here suggest that metabolic genes can affect sleep regulatory pathways, implicating a bidirectional relationship between metabolism and sleep. ***PC***

Tension and polarity

Most epithelial tissues display planar cell polarity (PCP), which refers to directionality in the axis orthogonal to the apical-basal axis. In the *Drosophila* wing, cells exhibit PCP in the proximal-distal axis during late pupal stages. However, the cellular and molecular mechanisms that generate global PCP in this tissue are not well understood. Previous studies suggested that PCP proteins are initially randomly distributed and become polarized along the proximal-distal axis late in the pupal stages. Suzanne Eaton and colleagues now report that PCP is actually evident earlier in development (*Cell* **142**, 773–786, 2010). At this early stage, PCP is observed in a radial direction that points toward the wing margin. The authors further show that contraction of cells in the wing hinge exert mechanical forces that lead to remodeling of wing blade cells, eventually leading to PCP in the proximal-distal axis. The atypical cadherin Dachsous (Ds) is not required for wing hinge contraction but is required for generating proximal-distal polarity in the wing blade. Contrary to previous views that the atypical cadherins Fat (Ft) and Ds directly act on PCP signaling proteins, the authors propose that Ft and Ds influence proximal-distal polarity by affecting cellular remodeling processes such as cell elongation and oriented cell divisions. *PC*

Corneal dystrophy risk locus

Albert Edwards and colleagues (*N. Engl. J. Med.* **363**, 1016–1024, 2010) report the discovery of common variants at chromosome 18q21.2 that are strongly associated with Fuch's corneal dystrophy (FCD), an age-related progressive condition marked by reduced corneal transparency and vision loss. The authors performed a genome-wide association study of FCD in individuals of European ancestry and identified a cluster of SNPs near *TCF4* associated with risk of the disorder. The association between the lead SNP at this locus and FCD was replicated in an independent collection of subjects, with a combined P of 2.34×10^{-26} and an estimated per-allele odds ratio of 5.47. Fine mapping of the region identified multiple risk alleles near *TCF4* independently associated with FCD. *TCF4* encodes a member of the ubiquitously expressed class I basic helix-loop-helix transcription factors and is a plausible candidate for mediating the effects of this locus on FCD risk. Notably, the magnitude of the effects associated with risk alleles at this locus is large compared to those identified for many other common diseases, suggesting that these findings may be useful for identifying individuals at high risk for developing FCD. *KV*

Written by Orli Bachall, Pamela Colosimo, Emily Niemitz & Kyle Vogan

Ovarian cancer sequencing

Two sequencing studies identify mutations in *ARID1A*, encoding a component of the SWI-SNF chromatin remodeling complex, in ovarian cancer. Nickolas Papadopoulos and colleagues report whole-exome sequencing of eight ovarian clear-cell carcinoma samples (*Science* published online, doi: 10.1126/science.1196333, 8 September 2010). They identify four genes with mutations in at least two tumors and validate these findings using Sanger sequencing in an additional 34 cases, including tumor and matched normal cells. The genes include *PIK3CA* and *KRAS*, oncogenes that were previously implicated in ovarian cancer, as well as two newly implicated genes, *PPP2R1A* and *ARID1A*. Over half of the ovarian cancer samples studied had mutations in *ARID1A*. In a related study, David Huntsman and colleagues report RNA sequencing of the transcriptomes of 18 ovarian clear-cell carcinomas and 1 cell line (*N. Engl. J. Med.* published online, doi: 10.1056/NEJMoa1008433, 8 September 2010). They identified mutations in *ARID1A* in six samples and followed this with targeted genomic resequencing of this gene in 210 ovarian carcinomas of various subtypes. They identified mutations in *ARID1A* in 65 of these samples, including 46% of the clear-cell carcinomas, 30% of the endometrial carcinomas and none of the high-grade serous carcinomas studied. Together, these studies highlight a role for *ARID1A* in the clear-cell and endometrial subtypes of ovarian cancer. *OB*

Gain of stability

Fascioscapulohumeral muscular dystrophy (FSHD) is genetically linked to contraction of D4Z4 subtelomeric repeats on chromosome 4, but how contraction of repeats causes disease has been unclear. Now, Sylvère van der Maarel and colleagues report the identification of linked genetic elements that take us a step closer to understanding the mechanism (*Science* published online, doi:10.1126/science.1189044, 19 August 2010). The authors previously showed that the D4Z4 contraction is only pathogenic on a specific genetic background. They also showed that the contraction of D4Z4 repeats is associated with repeat hypomethylation and loss of heterochromatic modifications. Now the authors show that the permissive background contains a polyadenylation signal sequence that stabilizes the *DUX4* transcript originating from the final D4Z4 repeat unit. The authors tested constructs from permissive and non-permissive genetic backgrounds, which confirmed the role of the polyadenylation sequence in promoting *DUX4* transcript stability. The authors also screened a collection of disease-permissive chromosomes from affected individuals as well as control chromosomes and confirmed that all of the disease-permissive chromosomes exclusively contained the polyadenylation signal. The authors propose a model in which D4Z4 repeat contraction causes an open chromatin confirmation that acts in concert with the polyadenylation signal to create toxic gains of *DUX4* transcript levels. ***EN***