

DAPK1 and chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) has high heritability relative to other cancers, suggesting that genetic predisposition can be important. Now, Albert de la Chapelle, Christoph Plass and colleagues have identified a putative tumor suppressor, *death-associated protein kinase 1 (DAPK1)*, that probably contributes to predisposition to familial and sporadic CLL (*Cell* 129, 879–890; 2007). The authors studied a single large family segregating CLL to identify a linked region on chromosome 9 and selected *DAPK1*, a positive mediator of apoptosis, as a candidate. Studies of sporadic cases of CLL indicated that the *DAPK1* CpG island is frequently hypermethylated and is accompanied by reduced expression of *DAPK1* in the majority of affected individuals. In the family with CLL, the CLL-linked haplotype showed reduced *DAPK1* expression and promoter hypermethylation, and sequencing of the haplotype revealed the presence of a single-nucleotide mutation in the upstream regulatory sequence. The authors identified another instance of this mutation in an unrelated individual with CLL, but they did not find the mutation in controls. Functional studies showed that the mutation increases binding of *HOXB7*, which represses *DAPK1* transcription. This work identifies a putative role for *DAPK1* and resistance to apoptosis in familial and sporadic CLL.

EN

Autophagy and genomic instability

Autophagy functions as a survival pathway, providing an alternative energy source to maintain normal metabolism in cells under metabolic stress. Cells in which autophagic functions are defective can give rise to tumors, which is paradoxical, given that the elimination of a 'survival' pathway would be expected to inhibit tumorigenesis. Robin Mathew and colleagues now provide the first evidence that cells in which autophagy is compromised have elevated chromosomal instability, providing a potential molecular explanation for the association between loss of autophagy and cancer (*Genes Dev.* 21, 1367–1381; 2007). The gene *Becn1* (beclin1) is required for autophagy, and the authors carried out a series of experiments in immortalized *Becn1*-deficient cells. They show that these cells have impaired recovery from metabolic stress, as well as higher levels of DNA double-strand breaks, centrosome and ploidy abnormalities and gene amplification. Cells lacking another autophagy gene, *Atg5*, also showed elevated DNA damage, suggesting that the effect was not limited to *Becn1*. Given the connection between autophagy and genomic instability, the authors suggest that pharmacologic activation of autophagy in tumor cells might provide a way to limit damage to the genome and inhibit cancer progression.

AP

ATR, stem cells and aging

A growing body of evidence suggests that DNA damage response genes are important for normal development and for maintaining tissue homeostasis in adulthood. Consistent with these findings, Eric Brown and colleagues (*Cell Stem Cell* 1, 113–126; 2007) now report that conditional inactivation of ATR, a key checkpoint kinase, in adult mice results in a broad spectrum of age-related phenotypes. To bypass the requirement for ATR during embryonic development, the authors gen-

erated mice carrying a floxed allele of *Atr* and a transgene expressing a tamoxifen-regulated Cre-ERT2 fusion protein. After transient exposure to tamoxifen at 8–12 weeks, mice developed hallmarks of premature aging in multiple tissues, including skin, hair, bone, thymus, heart and kidney. In a subset of tissues, the authors noted a marked loss of proliferating cells and a depletion of stem and progenitor cell compartments. In the intestine, individual stem cells that escaped Cre-mediated deletion were sufficient to replenish the damaged tissue, resulting in recovery of normal tissue architecture. The role of ATR in preventing premature aging in adult tissues explains the frequent occurrence of progeroid phenotypes in individuals with Seckel syndrome harboring hypomorphic loss-of-function *ATR* mutations.

KV

Complete selective sweeps

In order to identify genes subject to selection, a number of recent studies have searched for loci showing positive selection in the human genome. Now, Scott Williamson and colleagues present new analyses to detect complete selective sweeps in the human genome (*PLoS Genet.* 3, e90; 2007). They applied their methods, which involve searching for the spatial patterns of allele frequency consistent with a recent selective sweep, to Perlegen HapMap data sets, selecting 24 individuals in three populations (African American, European American and Chinese). The approach is based on comparing the fit of neutral and selective sweep models, for a given genomic region, using a composite likelihood ratio (CLR) test statistic. Notably, this method provides precise estimates of the location of the selected site, which will facilitate fine-mapping of selection targets. These analyses can be considered complementary to previous approaches, which have focused on partial selective sweeps. Reflecting this distinction, this study largely finds new candidates for selection not found in previous studies. Williamson and colleagues find evidence for selection in centromeric regions, pigmentation genes and olfactory receptors. Using simulations under different evolutionary models, the authors also tested for possible bias and showed that their methods were robust to demographic changes and variation in recombination.

OB

Risk of late-onset Alzheimer's disease

Recent data suggest that *APOE* is the major susceptibility gene for sporadic late-onset Alzheimer's disease (LOAD). A new study by Eric Reiman and colleagues suggests that variants in *GAB2*, encoding GRB-associated binding protein 2, can modify risk in individuals who are carriers of the *APOE* $\epsilon 4$ susceptibility allele (*Neuron* 54, 713–720; 2007). The authors genotyped more than 500,000 SNPs in three cohorts of brain or blood donors, each with or without LOAD and stratified by *APOE* $\epsilon 4$ status. In the initial discovery sample, ten of the SNPs associated with LOAD with the lowest *P* values were located in *GAB2*. Six of these SNPs were confirmed in the replication cohorts, and five withstood Bonferroni correction, with the most highly associated SNP reaching a *P* value of 10^{-11} in the combined data. The associated SNPs failed to survive Bonferroni correction when data from $\epsilon 4$ carriers and noncarriers were analyzed together. One of the functions of *GAB2* is to activate the PI3K-Akt-Gsk3 pathway, which is known to promote phosphorylation of tau in neurofibrillary tangles. The authors show that siRNA against *GAB2* in cells increases tau phosphorylation, suggesting a plausible mechanism for the effect of *GAB2* variation on LOAD.

AP

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