Kinases join the chromatin party

Although protein kinases involved in signal transduction pathways are known to phosphorylate many targets, including chromatin and transcriptional machinery proteins, they are not typically thought to join the chromatin complexes that occupy downstream target genes. An exception is the yeast Hog1p kinase and its human homolog p38, which were previously known to associate with the chromatin of target genes and function as components of transcriptional complexes. Now, Richard Young and colleagues report that many kinases involved in signal transduction frequently associate with target genes (*Science* 313, 533–536; 2006). Using chromatin immunoprecipitation with microarray detection (ChIP-chip), the authors first confirmed chromatin association of Hog1p when its pathway was activated by osmotic stress. By searching for Hog1p binding genome-wide, they increased the number of known Hog1p-bound genes from the previously known seven targets to thirty-six. Then the authors went on to investigate other yeast mitogen-activated protein kinases. Using ChIP-chip, the authors detected binding of Fus3p, Kss1p and Ste5p to target genes upon pheromone signaling and binding of Tpk1p and Tpk2p to target genes upon cAMP signaling induced by exposure to glucose. Together, these results show that signaling pathways connect more directly to downstream targets than previously appreciated. ***EN***

Mechanism of Smo inhibition by Ptch

The Hedgehog (Hh) signaling pathway is regulated at the cell surface by the activity of two integral membrane proteins: Smoothened (Smo), which acts as a key positive effector of Hh signaling, and Patched (Ptch), which acts as a receptor for Hh and represses Smo signaling in the absence of Hh. Mounting evidence suggests that Ptch acts substoichiometrically to inhibit Smo activity, but the underlying mechanisms are poorly understood. New work from Maikel Peppelenbosch and colleagues (*PLoS Biol.* **4**, e232; 2006) now suggests that the inhibitory effect of Ptch on Smo is mediated by the Ptch-dependent secretion of vitamin D3 or by another closely related 3β-hydroxysteroid derivative, which acts non–cell autonomously to repress Hh signaling activity locally. Notably, vitamin D3 binds to the same site in Smo as cyclopamine, a well-studied pharmacological inhibitor of Hh signaling, and treatment of zebrafish embryos with vitamin D3 produces a spectrum of defects similar to those seen in *smo* loss-of-function mutants. The proposed mechanism, supported by a range of biochemical, pharmacological and genetic arguments, presents a unifying hypothesis to explain previously noted links between defects in Hh signaling and inherited disorders of sterol biosynthesis. *KV*

Indel map

Insertion and deletion (indel) variation is considered an important component of genetic variation. In *Drosophila* and *C. elegans*, studies have shown that indels account for approximately 16–25% of genetic polymorphisms, and human studies (including an indel map of chromosome 22) have suggested a similar range. Scott Devine and colleagues now present a genome-wide map of human indel variation, with over 415,000 unique indels (*Genome Res.* published online 10 August 2006; doi:10.1101/gr.4565806). The authors developed a new computational method to identify indels in the human genome and confirmed them through comparison with the chimpanzee genome sequence and the Celera human genome sequence. PCR-based validation showed an overall accuracy of 97.2% (209 of 215 tested) across included indel classes. The authors note that single–base pair indels initially showed low validation rates, and the final collection includes only double-hit single-base indels. Approximately 36% of the indels were found within promoters, introns or exons of known genes. The authors further estimated that approximately 15.6% of identified polymorphisms were indels (similar to previous estimates) and that this initial map includes about 27% of expected human indels. They also observed hotspots with two- to fourfold-higher levels of indel variation, often in the same region as characterized SNP hotspots, suggesting regions of generally elevated genetic variation. *OB*

Research Highlights written by Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan

Checking misfolded CFTR

The ΔF508 mutation in *CFTR*, which is responsible for most cases of cystic fibrosis, was first discovered nearly two decades ago. This mutation causes misfolding and degradation of the CFTR peptide during the process of insertion into the endoplasmic reticulum (ER) membrane, preventing the protein from reaching the cell surface, where it functions as a chloride ion channel. Individuals with low levels of functional CFTR have a mild phenotype, suggesting that treatments that allow CFTRΔF508 to escape degradation may have a therapeutic effect. A cytosolic ubiquitin ligase complex containing Hsc70 and CHIP was previously shown to target CFTRΔF508, but inactivation of this complex is insufficient to allow CFTRΔF508 to escape degradation, suggesting that it is targeted by another checkpoint. Now, Douglas Cyr and colleagues have identified another quality-control checkpoint that is responsible for recognizing misfolded CFTRΔF508 and targeting it for degradation (*Cell* **126**, 571–582; 2006). The authors identified an ER membrane-associated ubiquitin ligase complex containing RMA1, Ubc6e and Derlin-1. The complex is associated with the ER membrane and recognizes misfolded CFTR during translation. Defining the pathways through which CFTRΔF508 is degraded could be an important step in the development of an effective and long-awaited therapy for cystic fibrosis. *EN*

Together again

The primordial Hox gene cluster was quadruplicated more than 500 million years ago, with current evidence suggesting that the acquisition of new and distinct functions for each paralog has been a slow process. Petr Tvrdik and Mario Capecchi now report a series of experiments on *Hoxa1* and *Hoxb1* in mice that provide new insight into the evolution of Hox paralogs (*Dev. Cell* 11, 239–250; 2006). The authors generated mice with *Hoxb1* expressed from the *Hoxa1* locus, and *vice versa*. The slow divergence of these two paralogs was confirmed by the fact that the mice were essentially normal, with each paralog largely substituting for the other. Hemizygous $Hoxb1^{A1/-}$ mice exhibit a facial nerve hypomorphism, however, and $Hoxa1^{B1/B1}$ embryos some decreased viability, suggesting less-than-complete compensation of one for the other. To compare the relative importance of regulatory elements in *Hox1* evolution, Tvrdik and Capecchi created an additional line of mice in which the *Hoxb1* autoregulatory enhancer was inserted into the promoter of *Hoxa1*. This mouse experimentally reverses *Hox1* subfunctionalization, recreating the ancestral array of regulatory elements driving a single *Hox1* gene and providing complete and normal *Hox1* function even in the absence of *Hoxb1*. ***AP***