The stickleback strikes again

The publication in 2001 of a linkage map of the threespine stickleback (*Gasterosteus aculeatus*) promised to bring to bear the power of positional cloning on the genetic basis of evolutionary change. The establishment of this resource, and others, is now paying off with the report by Pamela Colosimo and colleagues on the identification of a variant influencing armor plate patterning (*Science* 307, 1928–1933; 2005). Marine sticklebacks have frequently colonized freshwater lakes, and this migration coincides with a marked reduction in the number of dorsal armor plates. Colosimo *et al.* used the linkage map to identify a quantitative trait locus of major effect for armor plate patterns. Linkage disequilibrium mapping with microsatellite markers was then used to narrow down the candidate interval to the gene encoding ectodysplasin, a member of the tumor necrosis factor family that is required in mammals for the proper development of a number of ectodermal derivatives. Notably, low-plated sticklebacks carrying a mouse ectodysplasin transgene developed extra plates in at least a few cases. As the low-plated allele is present at a low frequency in natural populations over a broad geographical range, the authors argue that standing genetic variation can provide the raw material for rapid phenotypic change. ***AP***

Functionally relevant

Identification of functional elements in the human genome is a primary goal of comparative genomics. Comparison of orthologous regions has been a powerful approach, although it is limited by the number of available genomes at a close evolutionary distance from humans. Now, James Mullikin, Michele Clamp and colleagues explore the utility of low-redundancy comparative sequencing of related mammalian genomes in correctly aligning orthologous regions and identifying functional elements in the human genome (*Proc. Natl. Acad. Sci. USA* **13**, 4795–4800; 2005). By comparing seven mammalian genomes, they found that the proportion of high-quality reads that could be aligned to human sequence ranged from ~77% for dog to 36% for hedgehog. With a mouse genome of 2× redundancy, >60% of the bases that align with finished sequence were able to be aligned, whereas an increase to 3× redundancy showed only an incremental improvement. These sequence alignments were used to identify previously described highly conserved regions, with accuracy that increased with the number of species sequenced and the redundancy, again with only incremental gains above 3× redundancy. On the basis of this analysis, the authors propose the sequencing of an additional 16 mammalian genomes at ~2× redundancy. *OB*

Annotation progress decimated

Transcripts of unknown function dominate the expression patterns of the human, mouse, fly and *Arabidopsis* genomes, raising questions about what proportion of these RNAs have biological functions and whether these expression patterns have consequences for the regulation of gene expression in the better-understood genes already recognized. Using eight cell lines, Cheng *et al.* (*Science* advance online publication, 29 March 2005; doi:10.1126/science.11086252) examined ~30% of the human genome in ten chromosomes by transcriptional profiling to 5-bp resolution. They concluded that the proportion of the genome that is transcribed (15.4%) is an order of magnitude larger that expected from existing annotation based on exons and gene prediction. More than half of the transcriptome comprises overlapping RNAs, but it is not known whether these result from transcription or from the activity of an RNA-dependent RNA polymerase. Overall, 19.4% were poly(A)$^+$ RNA and 43.7% were poly(A)$^-$. Another 36.9% were found in both poly(A)$^+$ and poly(A)$^-$ versions. On average, 31.8% of transcripts came from intergenic regions for which no annotated transcribed elements were known. If a gene is a contiguous stretch of nucleic acids producing a discrete cellular product, are these new entities genes? *MA*

Screening for Wnt components

Using an approach previously used to screen for genes involved in phenotypes such as cellular growth and cell morphology, Norbert Perrimon and colleagues report the results of a high-throughput genome-wide RNAi screen for regulators of the Wnt pathway (*Science* advance online publication, 7 April 2005; doi:10.1126/science.11093741). Luciferase reporter constructs were used to detect changes in Wnt signaling in cultured *Drosophila* epithelial cells following RNAi knockdown of most *Drosophila* genes. This approach, using cells in which the Wnt pathway is known to be active, allowed for identification of both positive and negative modulators. Included among the 238 candidates are 15 known pathway components and a plethora of genes not previously linked to the Wnt pathway and genes that have not been functionally characterized. Notably, the screen turned up several genes containing HMG boxes or homeodomains, indicating that Wnt pathway components, such as β-catenin, may interact with a diverse group of transcription factors. Select candidates were validated *in vivo* in *Drosophila* wing imaginal discs and confirmed to have evolutionarily conserved Wnt signaling function in human 293T cells. This work shows that new approaches to pathway discovery can expand our understanding of even extensively studied pathways. *EN*

Degrading Smad4

Smad4 is a key downstream mediator of TGF-β signaling and acts as a tumor suppressor in several human cancers. Smad4 turnover is regulated by ubiquitination, but the precise molecular mechanisms are unknown. Now, Stefano Piccolo and colleagues (*Cell* 121, 87–99; 2005) identify a new E3 ubiquitin ligase, Ectodermin, as an important regulator of Smad4 stability. Piccolo's group isolated Ectodermin in a screen for molecules that promote ectoderm formation when injected into *Xenopus* embryos. They show that Ectodermin is enriched in the prospective ectoderm and helps to restrict the mesoderm-inducing activity of TGF-β–related ligands to the appropriate germ layer. Ectodermin attenuates TGF-β signaling by binding directly to Smad4 and targeting it for degradation through the ubiquitin-proteasome pathway. Notably, Ectodermin is also expressed in human colon in cells near the crypt base and in precancerous and cancerous lesions. Using RNAi to deplete Ectodermin from several cancer cell lines, Piccolo and colleagues show that Ectodermin attenuates the antiproliferative effects of TGF-β signals. These results imply that blocking Ectodermin function could help stabilize Smad4 levels *in vivo*, thereby restoring the cytostatic effects of TGF-β signals in tumors that retain wild-type Smad4 function. ***KV***

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