Glioma methylation

Glioblastoma is a highly malignant type of brain tumor, and individuals with the disease have a median survival time of only 15 months. The Cancer Genome Atlas Research Network (*Cancer Cell* published online, doi:10.1016/j.ccr.2010.03.017, 15 April 2010) now reports a distinct subtype of glioma with specific molecular and clinical features. The authors analyzed DNA methylation in 272 Cancer Genome Atlas glioblastoma tumors and found that 24 of the samples displayed similar methylation profiles, which were characterized by CpG island hypermethylation at a subset of genes and increased CpG island methylation throughout the genome. Of 1,550 unique genes assayed, 1,520 showed hypermethylation and 30 showed hypomethylation at their promoter region. Nearly 90% of these 24 glioma CpG island methylation phenotype (G-CIMP) tumors also displayed a proneural gene expression profile. Individuals with G-CIMP tumors were, on average, 20 years younger compared to individuals with non–G-CIMP proneural tumors (median age of 36 years compared to 59 years) and had longer survival times (median survival of 150 weeks compared to 42 weeks). To validate the G-CIMP loci, the authors assayed DNA methylation at 7 hypermethylated loci in 208 additional tumors and identified 7.6% of them to be G-CIMP positive. They also analyzed 153 low-grade gliomas for G-CIMP methylation. The authors found that G-CIMP status was predictive of the survival of individuals with glioma. ***PC***

Ciona *cis*-regulatory networks

The regulatory networks that control gene expression during development are in large part governed by sequence-specific binding of transcription factors to the genome. Yutaka Satou and colleagues report an analysis of gene regulatory networks that specify endomesoderm tissue in the early embryo of the simple chordate *Ciona intestinalis* (*Development* **137**, 1613–1623, 2010). The authors performed chromatin immunoprecipitation (ChIP) on 11 core transcription factors important for endomesoderm specification. Comparison of the ChIP data with previous gene knockdown experiments showed that 58 of 76 previously known interactions are direct; 251 new interconnections were also found, suggesting that these 11 transcription factors are tightly interconnected. To validate the network connections, the authors overexpressed and knocked down MyoD, Brachyury and Twist-like1 expression and showed that expression levels of approximately half of their respective target genes were altered. The authors suggest that most transcription factor–DNA interactions have major effects on the regulatory control of their target genes. *PC*

c-Myc and RNA polymerase pausing

Promoter-proximal pausing of RNA polymerase II (polII) is an established regulatory mechanism that affects the expression dynamics of some genes. Now, Rick Young and colleagues report a genome-wide investigation of pausing-mediated regulation in mouse embryonic stem cells (*Cell* **141**, 432–445, 2010). Using chromatin immunoprecipitation (ChIP) sequencing, the authors profiled the genomic localization of polII using antibodies against the N terminus, phosphor-serine 5 and phosphor-serine 2, the polymerase-pause factors NELF and DSIF, and the elongation factor PAF1. Their analyses show that polII occupies the promoter-proximal region of the majority of genes in embryonic stem cells, regardless of whether the genes are actively transcribed or not. Promoter-proximal sites are occupied by polII, NELF and DSIF, and the release of polII pausing at active genes requires the pause release factor P-TEFb. The authors further investigate the role of the c-Myc transcription factor, which occupies about a third of the active genes in embryonic stem cells and is a key regulator of embryonic stem cell self-renewal and proliferation, in the regulation of transcriptional pausing in embryonic stem cells. The authors show that the c-Myc/Max heterodimer associates with P-TEFb and regulates polII pause release at c-Myc target genes. *EN*

Neandertal genome

Svante Pääbo and colleagues report a draft sequence of the Neandertal genome of three females who lived in Croatia over 38,000 years ago (*Science* **328**, 710–722, 2010). The analyzed DNA was isolated from bones recovered in the Vindija Cave in Croatia. The mitochondrial genomes of two of these individuals have previously been reported. Sequencing using Roche 454 and Illumina GAII platforms yielded 5.3 gigabases of Neandertal DNA sequence and an average 1.3-fold sequence coverage. The authors also sequenced the genomes of five present day humans, all at 4–6-fold coverage, using Illumina GAII; the individuals scanned included a San from Southern Africa, a Yoruban from West Africa, a Papua New Guinean, a Han Chinese and a French individual from Western Europe. They report a screen for positive selection in early modern humans, looking for sites where Neandertals lacked the derived alleles found in present-day humans. They identified 212 genomic regions containing putative selective sweeps, representing regions in which Neandertals carried fewer of the derived alleles than expected. Neandertals and modern humans were estimated to have diverged 270,000–440,000 years ago. The Neandertals were found to share more genetic variation with non-Africans in comparison to Africans, suggesting that they are more closely related. *OB*

X-chromosome exome sequencing

Leslie Biesecker and colleagues have used targeted exon capture and sequencing to identify the cause of a rare X-linked developmental syndrome (*Am. J. Hum. Genet.* published online, doi:10.1016/j.ajhg.2010.04.007, 6 May 2010). The disorder, known as TARP syndrome, is marked by early lethality and multiple congenital anomalies, including craniofacial and cardiac defects. The authors studied two families affected by this syndrome and identified a large candidate linkage region on the X chromosome spanning nearly 28 Mb. To find the causal mutations, the authors performed targeted capture and sequencing of the X-chromosome coding sequences of one female carrier from each family. They then applied a series of filters to the sequence data and identified a single gene, *RBM10*, harboring nonsense or frameshift mutations that segregated with carrier status in each family. Expression studies in mouse embryos showed that the orthologous gene, *Rbm10*, is expressed in the first and second branchial arches and in the limb and tail bud regions, which correlates well with the malformations seen in TARP syndrome. The authors conclude that targeted exon capture can be an efficient strategy to identify disease-causing mutations for rare disorders. ***KV***

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