Mimivirus genome

Didier Raoult and colleagues report the genome sequence of Mimivirus, first isolated seven years ago from amoebae growing in the cooling tower of a hospital in Bradford, England (*Science* advance online publication 14 October 2004; doi:10.1126/science1101485). The 1.18-Mb viral genome is contained in a particle ~400 nm in diameter—a size comparable to that of small bacteria. The genome sequence reveals some remarkable features. The scope of the translational apparatus found in Mimivirus is unprecedented for a virus, with six tRNA-like genes, four aminoacyl-tRNA synthetases and a number of translation initiation factors. Other firsts for double-stranded DNA viruses include certain DNA repair enzymes, enzymes related to glutamine metabolism, nucleoside diphosphate kinase and homologs of certain bacterial heat-shock proteins. The authors argue that the number of enzymes and metabolic pathways encoded by Mimivirus "blurs the established frontier between viruses and the parasitic cellular organisms with small defective genomes". Does Mimivirus, as Raoult *et al.* suggest, define a new branch of life? ***AP***

Predicting miRNA targets

MicroRNAs (miRNAs) encoded by 1% of human genes may regulate 10% of the translated genome. John *et al.* (*PLoS Biol.* **2**, e363; 2004) arrived at this conclusion by applying an updated algorithm that makes use of systematic position-specific rules and interspecific conservation. They used 218 known mammalian miRNAs to scan for position-specific sequence complementarity in a number of vertebrate 3′ untranslated sequences (UTRs). Transcripts with complementary sites were then examined for orthologs having position-conserved target sequences in mammals and in fish. This procedure yielded 2,273 UTRs bearing targets in at least two mammalian species and exhibiting 90% target site conservation. The authors noted a fivefold enrichment of miRNA targets among the mRNAs bound by the fragile X mental retardation protein, FMRP. This observation is cited as support for the hypothesis that miRNAs might act as sequence-specific components of ribonucleoprotein particles that interact with mRNAs. Opportunities for regulation are manifold, as one miRNA can target many genes and, conversely, one gene can have sites for binding multiple miRNAs. Finally, 240 vertebrate targets were conserved between mammalian and fish, including Hox genes and genes involved in axon guidance. *MA*

New gene associated with Parkinson disease

Although familial forms of Parkinson disease are rare, identifying the genetic lesions underlying them can provide insights into the disease mechanism and offer clues to the etiology of the more common sporadic forms of the disease. Coro Paisán-Ruíz and colleagues (*Neuron* advanced online publication, 22 October 2004; doi: 10.1016/S08966 27304006890) report mutations in a gene on chromosome 12 associated with an autosomal dominant form of Parkinson disease. They studied four Basque families showing linkage to the region and identified a common haplotype spanning 2.6 Mb carried by all affected individuals. By sequencing genes in the critical interval, they identified a missense mutation (R1396G) in a putative kinase-domain–containing gene (*LRRK2*, also called *PARK8*) carried by all affected family members. They then examined a fifth, unrelated UK family showing linkage to the region and found a second *LRRK2* missense mutation (Y1654C) segregating with the disease in this kindred. By screening an additional 137 individuals with Parkinson disease from the Basque region, Paisán-Ruíz *et al.* discovered another 11 cases carrying the same R1386G mutation, six of whom had a positive family history for the disease. Based on their findings, the authors suggest that mutations in *LRRK2* could contribute to sporadic cases of Parkinson disease in the general population. *KV*

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

Exposing risk factors

"A large number of people exposed to a small risk may generate many more cases than a small number exposed to a very high risk," according to the often-quoted finding of epidemiologist Geoffrey Rose. Anthony Rogers and colleagues apply this theory to analysis of global health risks and similarly find that most risk factor–attributable disease is caused by moderate exposure (*PLoS Medicine* **1**: e27; 2004). The World Health Organization's global burden of disease project has surveyed the disease burden among population subgroups, defined by demographic as well as socioeconomic factors. Here, the authors examine exposure to 26 risk factors in 14 epidemiological subregions. They calculate the proportion of risk factor–attributable disease burden in different population subgroups defined by age, sex and exposure level. A large proportion of risk factor–attributable disease occurs among those with only moderate (as opposed to extreme) exposure to the risk factor. This suggests that interventions reducing exposure to risk factors on a population-wide basis, even by only a small amount, may be the most beneficial in reducing disease burden. Further, the distribution of risk factor–attributable disease varies by region, highlighting the importance of determining not only the mean exposure to a risk factor, but also the entire distribution. *OB*

The t loop: a double-edged sword

T loops, the protective structures at the ends of telomeres that tuck the 3′ overhang into the duplex TTAGGG repeat, are thought to prevent chromosome fusion by preventing nonhomologous end joining machinery from accessing the chromosome end. Conversely, t loops present a potential danger because they resemble the Holliday junction, an intermediate in homologous recombination. Another protective component of telomeres is TRF2, a protein that binds TTAGGG repeats and is thought to aid in the formation of t loops. TRF2 prevents activation of DNA damage pathways and is critical for the prevention of nonhomologous end joining. A study by Richard Wang and colleagues (*Cell* 119, 355–368; 2004) describes a mutated *TERF2* allele that retains the ability to bind telomeres, protecting them from nonhomologous end joining, but induces t-loop deletion by homologous recombination. When cells express the mutated *TERF2* allele, deletions occur rapidly, shortened telomeres and t loop–sized telomeric circles are generated and senescence is induced. Additionally, a DNA damage response is activated that requires XRCC3, a protein associated with Holliday junction resolution. As low levels of telomeric circles were detected in uninfected cells, telomere deletion by homologous recombination may be a feature of normal telomere metabolism. These results implicate t loops in telomere attrition and indicate that protective t loops also present a danger to the chromosome end. ***EN***