Resisting infection

Mice lacking MyD88, an adaptor protein that acts downstream of Toll-like receptors (TLRs) and interleukin-1 receptors (IL-1Rs), are susceptible to a broad range of bacterial, viral and fungal infections, highlighting an essential role for this pathway in host defense. In contrast, Jean-Laurent Casanova and colleagues (Science 321, 691-696; 2008) now report that humans with biallelic loss-of-function mutations in MYD88 are susceptible to a much narrower range of bacterial infections, supporting prior evidence that humans have alternate mechanisms in place to resist most pathogenic challenges. Previously, the same group reported (Science 299, 2076-2079; 2003) that individuals with inherited deficiency in IRAK-4, another downstream component of the TLR and IL-1R signaling pathways, were susceptible to pyogenic bacterial infections, such as invasive pneumococcal disease, but not other infections. Extending this observation, Casanova and colleagues now report that individuals with MyD88 deficiency show a spectrum of susceptibility to pyogenic bacteria very similar to that associated with IRAK-4 deficiency. These findings reinforce the view that the protective role of MyD88 and IRAK-4 in humans, although critical for resisting some lifethreatening infections, is redundant with other host defense pathways for restricting most types of infectious disease. KV

α 2-chimaerin and neuron pathfinding

Duane's retraction syndrome (DRS) is an eye movement disorder caused by aberrant innervation of extraocular muscles by cranial motor neurons. DRS occurs sporadically in about 0.1% of the general population, and can also occur as a familial trait. Now Elizabeth Engle and colleagues report the identification of missense mutations in CHN1 in seven families with dominantly inherited DRS (Science 321, 839-843; 2008). CHN1 encodes two isoforms, α1- and α2-chimaerin, of Rac guanosine triphosphataseactivating protein (RacGAP) signaling proteins that downregulate Rac activity. Three of the DRS-associated mutations alter amino acids specific to α 2-chimaerin, leading the authors to propose that the phenotype is caused by altered α 2-chimaerin function. Using cell culture systems, the authors showed that the missense mutations cause increased RacGAP activity of α 2-chimaerin, consistent with a gain-of-function mechanism. The authors then tested whether overexpression of $\alpha 2$ -chimaerin *in vivo*, in the embryonic oculomotor nucleus in the developing chick, caused aberrant oculomotor nerve development. They found that the oculomotor nerve axon failed to innervate its target muscle in embryos overexpressing wild-type or mutant α 2-chimaerin. This work reveals a function for α2-chimaerin in ocular motor neuron pathfinding. EN

Assortative mating and deafness

In his 1898 treatise *Marriages among the Deaf in America*, Edward Allen Fay collected family history data from 4,471 nineteenth-century marriages of deaf individuals. These data were re-analyzed by Rose in 1975, who reported that 4.2% of the matings were 'noncomplementary' (only capable of producing deaf offspring). Following up on a previous proposal that the large proportion of nonsyndromic deafness caused by mutations at the *DFNB1* locus (30–40%) might be attributable to assortative mating, Kathleen Arnos and colleagues report on an informative dataset of alumni of Gallaudet University, a school for deaf and hard-of-hearing

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students (*Am. J. Hum. Genet.* **83**, 200–207; 2008). On the basis of an analysis of 311 matings between deaf individuals, the authors report that 23% were noncomplementary, an increase of more than fivefold over the previous century. They also find a statistically significant linear increase in the frequency of mutations in *GJB2* and *GJB6*—the two genes at the *DFNB1* locus—when the alumni were partitioned into three 20-year birth cohorts. Arnos *et al.* argue that assortative mating—specifically for the use of American Sign Language—has in a relatively short time resulted in this increase in *DFNB1*-related deafness. They also note that the increasing use of cochlear implants could reverse this trend. *AP*

Genetic diversity

Demographic inference based on SNP variation in public databases can be complicated by ascertainment biases associated with SNP discovery and population sampling. With the aim of establishing a genetic variation database useful for more accurate inference of human demographic history, Michael Hammer and colleagues report a resequencing survey of intergenic regions in six populations of the Human Genome Diversity Panel (HGDP) (Genome Res. 18, 1354-1361; 2008). The authors sequenced 40 intergenic regions, selected to be at least 50 kb away from the nearest gene and totaling about 112 kb on the autosomes and 98 kb on the X chromosome, in each of 90 samples from the HGDP. They identified 1,658 SNPs, over half of which were unique to a single population. Higher levels of nucleotide diversity within populations as well as greater differentiation between populations were observed, compared to previous databases. Their dataset shows good coverage relative to comparable HapMap populations, with 98% of HapMap SNPs from the phase II dataset found in the HGDP resequencing study. However, only 20% of SNPs detected here were represented in comparable HapMap populations, and as expected, lower-frequency SNPs were not represented. For SNPs with MAF > 10% in the HGDP study, 56% were found also in the HapMap database. OB

Disease-specific stem cells

Somatic cells can be reprogrammed to produce induced pluripotent stem (iPS) cells by introducing a set of transcription factors linked to pluripotency. Now George Daley and colleagues report the production of iPS cells from individuals with ten mendelian or complex genetic disorders (Cell 7 August 2008; doi:10.1016/ j.cell.2008.07.041). The authors produced iPS cells from dermal fibroblasts or bone marrow-derived mesenchymal cells from individuals with Down's syndrome, adenosine deaminase deficiency-related severe combined immunodeficiency, Shwachman-Bodian-Diamond syndrome, Gaucher disease type 3, Duchenne muscular dystrophy, Becker's muscular dystrophy, Huntington's disease, Parkinson's disease, and type 1 diabetes mellitus, and from a carrier for Lesch-Nyhan syndrome. They confirmed the derivation of pluripotent cells by in vitro differentiation into embryoid bodies and by teratoma formation in immunodeficient mice. Because iPS cells can recapitulate human tissue formation in vitro, these cells will provide a resource for investigations into disease mechanisms, as long as the cells can be differentiated into relevant somatic cell or tissue types. This will be particularly useful for diseases where mouse models do not recapitulate human phenotypes. The authors note that the Harvard Stem Cell Institute intends to establish a Core Facility for the production of disease-specific iPS cell lines and for making these cells available to the research community. EN