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With this multitude of inhibitors, say Griffin, Druker and Hochhaus, prospects for CML patients are improving even further. And what is particularly exciting, adds Druker, 'is the speed at which inhibitors are being developed. Imatinib has only been on the market for four years and the first resistance to it was reported the same year. Yet two potentially promising drugs that can overcome resistance are already entering phase II trials.'

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Genetic origin of the AIDS epidemic

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TRIM5α, a host cell restriction factor found in human and non-human primates, is a natural cellular defense against retroviral invaders, most notably HIV-1. But whereas Old World monkeys and humans share similar versions of the gene, the simian version blocks HIV-1 infection prior to reverse transcription, halting infection in its tracks. Human TRIM5α cannot, leaving us wide open to HIV-1 infection and eventual progression to AIDS.

A crucial mutation

Now, virologist Jonathan Stoye and colleagues at the National Institute for Medical Research in London, UK have discovered that a single amino acid difference in the human TRIM5α gene, compared with the HIV-resistant rhesus monkey version, is partly to blame for the greatest epidemic to hit humans in the modern age [1]. Constructing chimeras of human and rhesus monkey TRIM5α gene sequences allowed Stoye's group to map and identify the regions involved in HIV-1 restriction. Most astonishingly, however, changing a single amino acid in human TRIM5α to its simian counterpart conferred HIV-1 resistance.

Joseph Sodroski and his team at Harvard University, USA, first described TRIM5α last year [2], showing that TRIM5α influenced HIV-1 susceptibility in a species-specific manner. Although HIV-1 could efficiently enter cells of Old World monkeys, the virus encounters the monkey TRIM5α, resulting in uncoating of the viral capsid prior to reverse transcription occurring. Human TRIM5α was not able to do this sufficiently to block infection.

The rest is history

'If this single change had not occurred, we probably never would have had AIDS in the first place,' says Stoye. 'It shows how susceptible we are to very small changes.'

John Coffin, a virologist at Tufts University, Boston, MA, agrees. 'Had a gene like the rhesus gene been present [in humans], then HIV-1 could not have made it into the human population.'

Still, there are no known humans possessing a TRIM5α containing the protective amino acid, even in the face of selective pressure. 'It's probably unlikely that there are humans that carry this mutation,' says Stoye. 'A small change allows the human protein to block HIV-1,' says virologist Greg Towers, University College London, UK. 'In future, we might imagine a human population that is able to block HIV-1 the way old world monkeys do.'

'Retroviruses have probably forced the evolution of defense mechanisms such as Trim5α,' explains Paul Bieniasz, a virologist at the Aaron Diamond AIDS Research Center in New York, USA. Indeed, the sequence surrounding the amino acid in question appears to have had selective pressures acting it, in what were probably epidemics of retroviruses, distinct from HIV-1, that are long since extinct, he explains. Furthermore, TRIM5α is not the only such host defense mechanism.

But results from other groups suggest that other amino acids may similarly be involved. 'This is clearly an important amino acid but it is not the only one,' says Bieniasz. He and his team have recently identified motifs important for restriction activity.

Similarly, Sodroski and colleagues most recently described three amino acid differences that they believe account for the difference in anti-HIV-1 potency between humans and rhesus monkeys. (ref 3) In a related paper published early online, Harmit Malik and colleagues at the Fred Hutchinson Cancer Research Center in Seattle, WA, examine the genetic differences in TRIM5α among species, suggesting that TRIM5α evolution has been driven by antagonistic interactions with early retroviruses that appeared on the evolutionary scene long before lentiviruses like HIV-1 arose [4].

Novel anti-HIV therapeutics

Understanding how TRIM5α interacts with HIV-1 is an area of particular focus now. Knowledge of this interaction could have important therapeutic implications, explains Coffin, by permitting identification of compounds that mimic Trim5α binding to the viral capsid proteins.

Stoye says a gene-based approach is another potential therapy, once efficient gene delivery methods come to fruition. 'If there is a case where one might contemplate gene therapy for an infectious disease, then this might be one,' he says. Such an approach

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could entail introducing a TRIM5α gene encoding the HIV-resistant protein, with the aim of repopulating a generation of cells capable of resisting infection, thereby preventing progression to AIDS, he explains.

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Untangling the patterns of genetic variation

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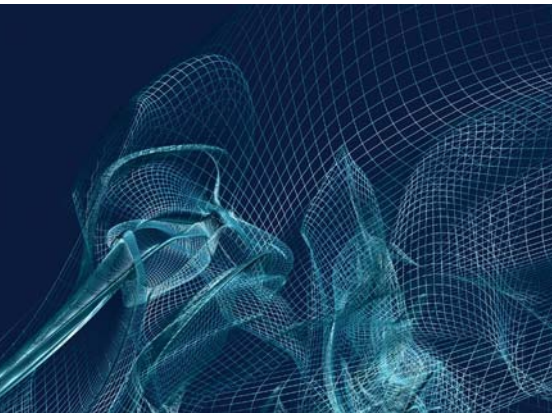
Scientists involved in the international HapMap project have completed a map of 1 million common markers of genetic variation across five human populations. Efforts are now underway to create an even denser map, with one single-nucleotide polymorphism (SNP) signpost every 600 bases. The data provide scientists with an essential tool for the development of more effective, individualized treatments.

An embarrassment of riches

The HapMap is a follow-on from the Human Genome Project. 'It grew out of the realization that there was an embarrassment of riches in the SNP databases,' says bioinformaticist Lincoln Stein at the Cold Spring Harbor Laboratory (Cold Spring Harbor, NY, USA), who is a principal participant in the HapMap project. 'The public projects had been so successful in finding SNPs that there were now over 8 million SNPs in the public databases.' However, information was lacking on the frequency of these variants and how the frequencies vary between different populations. Moreover, recent studies found a lot of redundancy in SNP databases [1]. Therefore, the International HapMap Consortium – a public–private partnership of scientists and funding agencies from the USA, the UK, Canada, China, Japan and Nigeria – was formed in October 2002 to define a structure of all this variation.



The human genome can be parsed into DNA regions within which little recombination has occurred – the so-called haplotype blocks. The SNPs in such a haplotype block are strongly associated with each other, whereas the association with other SNPs is relatively weak. Looking for these patterns, which are highly conserved across populations, the International HapMap Consortium began genotyping sequence variants of 270 DNA samples from populations with Northern and Western European, Chinese, Nigerian and Japanese ancestry. The resulting haplotype map tells researchers which SNPs describe the variation in a specific genomic region.

Customized medicine

'The primary goal is to make disease-gene finding faster and to help develop genetic-based tests that will indicate the best therapy for different individuals, in order to make possible this idea of customizing medicine to a person's genetic background,' notes Stein.

The $130 million project, designed to provide 1 million markers of common variation, was due to be completed in September this year, but thanks to technological advances during its course, it was completed half a year before schedule. The Affymetrix spin-off company Perlegen Sciences (Mountain View, CA, USA) now received $3.3 million funding to genotype another 4.6 million SNPs from publicly available databases. By September this year, they aim to add information on 2.25 million additional SNP signposts to the freely accessible HapMap databases (www.hapmap.org; www.ncbi.nlm.nih.gov/SNP; http://snp.ims.u tokyo.ac.jp). 'We are delighted that we get to triple the size of the HapMap without tripling the cost,' says Stein. 'It is typical of the genome project, that the science drives the technology and the technology drives the science.'

The HapMap set that has been done so far clearly has gaps in it, says Douglas Easton, a Cancer-Research-UK-funded epidemiologist at the University of Cambridge (Cambridge, UK). 'The new set [will be] much denser. The idea is to try and get to the point where one is as confident as possible that all the common variants have been identified.' This could help our understanding of the molecular basis of common diseases, like cardiovascular disease and diabetes. However, Easton adds that there might be a lot more rare variants to look for; they are much harder to approach and are not evaluated in the HapMap project.

New targets

Researchers worldwide are already using the current data by comparing the haplotype patterns of different groups of people. Much of that research focuses on the study of genes that have been linked to disease or drug metabolism. But scientists have also begun to design experiments that look at the whole genome. If an association study finds a certain haplotype more often in people with a given disease or drug response, researchers will narrow down their search to that genomic region to find the specific genetic variant involved in the disease or drug response, with the tag SNPs serving as signposts indicating that the culprit variant lies nearby. Easton predicts that these association studies will be going on over the next 2–3 years. 'Hopefully, out of that will come new targets for new therapies,' he concludes.

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