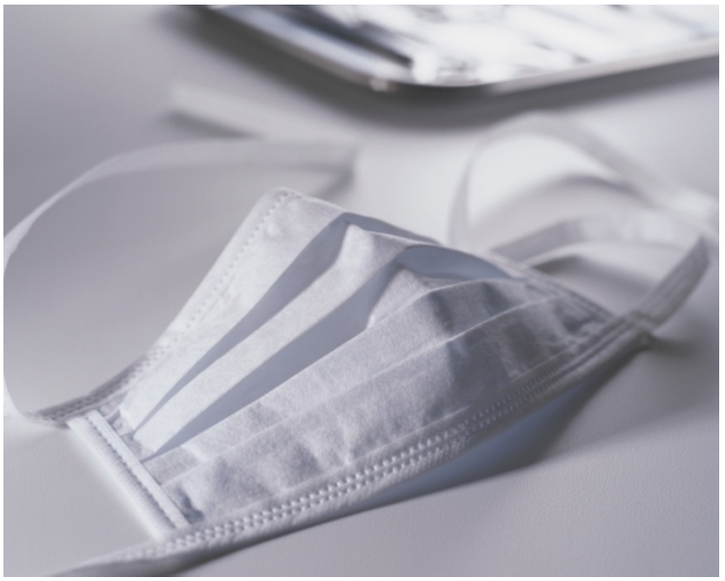
RNA INTERFERENCE

Interfering with infection



RNA interference (RNAi) — double-stranded RNA-mediated sequence-specific gene silencing — is used by developmental biologists to modulate gene expression, but nature, it is thought, uses it as a defence against transposition and viral infection. Several labs have been interested in using RNAi to control viral infection and we are now witnessing the first fruits of this research — three reports in *Nature* and one in *Nature Medicine* show that short interfering (si) RNAs (molecules that mediate RNAi in mammals) can inhibit infection by HIV-1, polio and hepatitis C viruses in a sequence-specific manner, thus offering the promise of antiviral therapy.

By targeting several regions of the HIV-1 genome, Jacque *et al.* showed that siRNAs mediate viral genome degradation and cause downregulation of viral gene expression. Contrary to previous studies, they reported that RNAi works even when the viral genome is contained within the nucleoprotein complex. They also show that intracellularly made siRNAs (transcribed from a plasmid) work well, providing possible ways for delivering gene-therapy agents against HIV. Novina *et al.* extend this work and show that RNAi against CD4s, and other cell-surface receptors that HIV uses to enter host cells, decreases virus entry. Their results reveal that RNAi effects are dose dependent and that the HIV genome remains a target for RNAi even after its integration into the host genome.

Gitlin *et al.* showed that RNAi drastically reduces polio infection in HeLa cells. While analysing the antiviral effects of siRNAs over a course of viral infection, they found siRNA-resistant viruses that turned out to carry silent base-pair mismatches in the siRNA complementary sequences. The authors argue, therefore, that if RNAi is to be used for therapeutic purposes, siRNAs

HUMAN GENETICS

A surprise in asthma research

Asthma is characterized by chronic inflammation of the airways that results in breathing difficulties, coughing and wheezing. So far, there have been reports of its linkage to at least nine chromosomes, and a paper by Keith and colleagues in *Nature* now reports linkage to a tenth. So, why should we get excited? Keith and colleagues show that, through careful and thorough work, it was possible to locate a novel asthma susceptibility gene — in this case, one that has a plausible role in the disease and so might encode a therapeutic target.

In this study, the authors carried out a multipoint linkage analysis on Caucasian families from both the United States and the United Kingdom. Definition of the 'asthma' phenotype is crucial, and, in this study, cases had to be diagnosed by a physician and to need asthma medication. Unexpectedly, the strongest linkage signal was to 20p13, a region not previously implicated by most large-scale asthma studies. However, the region on mouse chromosome 2 that is syntenic to human 20p13 is linked to bronchial hyperresponsiveness (BHR), which often occurs in asthma patients. Indeed, when the authors only considered the cases of asthma with BHR, the linkage signal in 20p13 got even stronger. So, the group constructed a physical map of the 2.5-Mb region with the strongest signal.

To find the right gene, the authors reanalysed the cases for association to SNPs and haplotypes (SNP combinations) in the 20p13 interval using a case–control study design. The strongest associations occurred in the *ADAM33* gene. The authors then went on to analyse some of their SNP markers in *ADAM33* in a family-based test for association, the TDT. Certain *ADAM33* alleles were significantly over-transmitted to asthmatic compared with non-affected offspring, especially when the tested phenotype was restricted to asthma with BHR. So, using several approaches, Keith and colleagues seem to have pinpointed quite robustly a novel susceptibility gene for asthma.

So, what does *ADAM33* have to do with asthma? The gene encodes a zinc-dependent metalloprotease, which the authors show is expressed in lung tissues. Such proteins could be important for remodelling the airway in response to injury, and it is conceivable that variation in the amount of functional *ADAM33* product leads to impaired remodelling and therefore chronic inflammation. No causative mutations in the gene have been reported, and we don't know whether variation in the abundance or activity of the ADAM33 protein is altered in the lungs of asthma patients. But, in the search for therapies to aid the ~5% of

Pollen — a common trigger for asthma.

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need to be designed against highly conserved parts of the viral genome.

Kay and colleagues went beyond the *in vitro* systems and genetically engineered mice that express siRNAs against hepatitis C RNA to show that this technique also works well *in vivo* to prevent viral replication.

After this bumper crop of promising results, it remains to be seen how close we are to RNAi-mediated antiviral therapy. Because siRNAs tap into natural gene-silencing pathways, a new form of intracellular immunization against viral infection might be just around the corner.

Magdalena Skipper

References and links

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humans affected with asthma, we need all the targets we can find.

Chris Gunter, Associate Editor, Nature

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Van Eerdewegh, P. *et al*. Association of the *ADAM33* gene with asthma and bronchial hyperresponsiveness. *Nature* 10 July 2002 (10.1038/nature00878)

WEB SITES
Asthma Gene Database: http://cooke.gsf.de/asthmagen/main.cfm
NCBI "Genes and Disease" on asthma: http://www.ncbi.nlm.nih.gov/disease/asthma.html

HAPLOTYPE MAPPING

Shortcut around the block

Until now, gene mappers have had to take the long road to finding disease genes, as combing the whole genome can be a lengthy and expensive undertaking. However, a shortcut could be opened up if, as some propose, the human genome turns out to be 'block-like', that is, consisting of DNA regions in which recombination is rare, bordered by recombination hot spots. The theory goes that disease genes could be tracked to one of several haplotypes (combinations of alleles) that define each block. If each haplotype can be identified by a small number of markers, mapping would become quicker and cheaper. However, some groundwork needs to be done before the 'haplotype mapping' approach can take off: the first is to assess properly the block-like structure of the genome. Two papers have done just that by empirically delineating the haplotype blocks in our genome. On the basis of the success of these two reports, the second step — using the haplotype map, or HapMap, to map disease genes of the human genome — should soon follow.

In the first study, Stacey Gabriel and colleagues used ~4,000 publicly available SNPs (single-nucleotide polymorphisms) to identify blocks in 51 autosomal regions — selected on the basis of having closely spaced SNPs and totalling 13 Mb, or ~0.4%, of the genome — and then compared them among four populations: Europeans, Asians, Africans and African Americans. The authors found 928 blocks, which, as expected, were shorter in the older, African populations, consistent with the view that blocks become eroded over time by recombination. The fact that few (3–5) common haplotypes were identified for each block, and that they could be uniquely identified with as few as 6–8 random markers was very reassuring, as was the fact that half of the haplotypes were shared by all four populations. Perhaps less encouraging was the finding that the average size of the blocks is quite small (11–22 kb), meaning that, to be useful, the HapMap might need to be built from up to a million SNPs.

A similar pattern was seen in a second study, by Dawson *et al.*, who used 1,500 publicly available SNPs and insertion/deletion polymorphisms to derive 59 haplotypes across the whole of chromosome 22. The size of blocks across this chromosome is quite variable: small stretches are interspersed with large (up to 800-kb) blocks in which recombination is low. As in the previous study, common haplotypes could be distinguished by genotyping very few (in this case, three) SNPs. A strength of this study was the use of family-based samples, which the authors show are a more informative source of haplotype information than are unrelated individuals.

Constructing a HapMap might therefore be technically feasible, but will it work? The arguments against using haplotype mapping to locate complex trait genes have been well rehearsed. The emphasis on common haplotyes (captured using common SNPs) presupposes that common diseases are caused by common variants and precludes the identification of rarer, and perhaps population-specific, alleles. Believers and non-believers alike will just have to await the formal test to see who is right.

Tanita Casci

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ORIGINAL RESEARCH PAPERS Gabriel, S. B. *et al*. The structure of haplotype blocks in the human genome. Science **296**, 2225–2229 (2002) | Dawson, E. *et al*. A first-generation linkage disequilibrium map of human chromosome 22. *Nature* 10 July 2002 (10.1038/nature00864)

WEB SITES
The SNP Consortium Ltd: http://brie2.cshl.org
The Centre d'Etude du Polymorphisme Humain (CEPH) genotype database: http://www.cephb.fr/cephdb

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