HIV – tailored to fit

Helen Dell, BMN News

New research on HIV shows that the virus mutates throughout its genome to evade each particular individual's immune system, report Australian immunologists. The results could have important implications for vaccine design, they say.

HIV infection

'The immune response to HIV infection is complex, involving many interacting pathways and components, and these pathways are influenced by both host and viral genetic factors,' said Frank Christiansen, Professor of Clinical Immunology at the Royal Perth Hospital in Perth, Australia (http:// www.rph.wa.gov.au/). But his latest study suggests that how the virus mutates after infection is a major factor in disease progression.

'What happens after HIV infection is the viral load goes up and then the immune response kicks in to bring the virus under some degree of control, but you do not completely eradicate the virus,' explained Christiansen. Eventually, the viral load levels off, reaching the so-called viral set point, where the protective immune response of the host is balanced against the viral capacity of the individual.

'The viral set point is relatively controlled for a period of time, but eventually the virus 'escapes' from the immune system and increases, and you get the onset of full-blown AIDS,' he said. He has been trying to identify the genetic factors that influence how this escape happens.

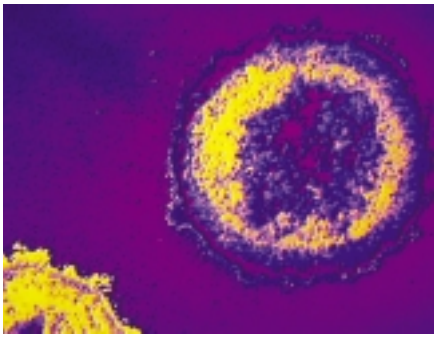
The great escape

The development of escape is clearly associated with specific viral peptide epitopes that are displayed on the surface of infected cells by class I human leukocyte antigen (HLA), he says. These epitopes should alert cytotoxic T lymphocytes (CTLs) to kill infected cells, but the HIV subverts this system to allow it to escape.

The HLA molecules have more that 50 different genetic variants, although each person will only have a few of these, and Christiansen's hypothesis was that the viral epitopes might adapt to fit the host's HLA in such a way that they trick the CTLs into thinking the cell was not infected. 'The HIV adapts to the CTL responses,' he said. 'We would expect that viral escape mutations would be evident as HLA-associated mutations.'

So, in work presented in Harrogate, UK, at the annual meeting of the British Society of Immunology (http:// immunology.org; 2–5 December 2003), Christiansen and his colleagues have sequenced the HIV virus present in 273 patients from Western Australia, and typed their HLA molecules. They also measured the patient's viral set point before initiating treatment. The virus sequence showed positions that varied a lot (polymorphic sites) and positions that seemed to be constrained to the consensus sequence. 'The areas of high constraint are associated with regions of structural or functional importance,' noted Christiansen.

Next, the researchers looked at whether particular HIV mutations were associated with particular HLA variants; that is, whether they were more or less likely to occur together in the same patient. The team found numerous associations, mostly positive, which tend to be at the polymorphic HIV sites. What is more, many of the associations are with known epitopes in the HIV viral



sequence. 'That was reassuring,' said Christiansen. 'What we were picking up were in fact the mutations of polymorphic regions in the epitopes.'

Global adaptation score

To find out whether the HIV was adapting to the host's HLA system, the researchers turned the experiment round slightly to measure the 'global adaptation score'. That is, for each of the patient's HLA variants, they looked at all the HIV polymorphic sites that are associated with that variant, and determined the percentage that are adapted to that HLA. 'We say the site is adapted if the polymorphisms are present at a site of positive association, or the consensus is present at a site of negative association,' explained Christiansen.

They then compared this to the patient's viral set point, to see how well the patient's immune system was coping with the infection, and found that for each patient, the more adaptation there is, the higher is the viral load. 'In some individuals, 80–100% of the polymorphic sites have been adapted,' pointed out Christiansen. 'The virus is almost completely adapted to the host's immune response, and these individuals have the highest viral set point.'

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HLA profiles

The difference in the viral load between people who are only 20–40% adapted and those who are 80–100% adapted suggests that this adaptation of HLA is more important than many other recognized host genome effects. 'These results provide evidence that host HLA is an important factor affecting on viral evolution,' says Christiansen.

'We think this has important lessons for vaccine design, in that the HLA profiles of individuals provide specific selective pressure for HIV mutation, and can be a very important genetic barrier to resistance,' he concluded. 'The ultimate vaccine design will require the consideration of the frequency of the HLA alleles in the [local] population, the likelihood of the virus adapting to them and the consequences of such adaptation.'

Professor Andrew McMichael, Director of the Medical Research Council (MRC) human immunology group at the John Radcliffe Hospital in Oxford, UK (http://www.oxfordradcliffe.nhs.uk/), is impressed by the work. 'I think it is very interesting in terms of the evolution of the virus and the variability of the virus,' he said.

But he has reservations about how practical it will be to design vaccines taking the results into consideration. 'I suppose what he's saying is that the virus is shaped by the HLA system in the local population. So for instance, in India and South Africa, the HLA systems that are common to each population will be different, and you would have to have a vaccine tailored for each,' he said. 'But there is a practical limit to how many vaccines you can actually make.'

Hottest news from the Cordia EuropaBio Convention 2003, 2–4 December 2003 in Vienna, Austria.

European biotech gets personal

Henry Nicholls, BMN News

It will take only 10–20 years for the realization of 'proper personalized medicine' for the prevention and treatment of cancer, claims a leading European oncologist.

It is inevitable that biotech will achieve this goal, says Karol Sikora, Professor of Cancer Medicine at the Hammersmith Hospital in London, UK (http://www.hhnt.org/), and a senior consultant to the pharmaceutical company AstraZeneca (http://www.astrazeneca.com).

The winds of change

The speed of change is not so predictable, he admits, but he predicts it will take between 10 and 20 years to realize the goal of personalized therapy for cancer.

Within about five years, says Sikora, routine genetic profiling should make it possible to identify those at risk of cancer long before there is any sign of a tumour. 'So far, nobody has tried to develop a drug for cancer prevention,' he said, while insisting that this will become integral to healthcare in the future.

There is one thing that could complicate the pace of change, warns Sikora. Most existing cancer drugs will reach the end of their patents in 2008, opening the way for competition from generic drugs. The resulting loss of revenue could lead to a shortfall in investment in current development, he fears.

Ripples in biotechnology

Sikora was speaking after a plenary session at the CORDIA–EuropaBio Convention, 2–4 December 2003 in Vienna, Austria – the first Europe-wide meeting specifically tailored for the biotechnology industry (see http:// www.cordia-forum.com). His predictions were echoed by fellow delegate Mary Harney, Ireland's Minister for Enterprise, Trade and Employment.

Europe is beginning to create significant ripples in biotechnology, says Harney. The UK, Germany and France have more than 1000 biotech companies backed by more than 40 universities and 10,0000 researchers, she told delegates in her keynote address. This makes up around a quarter of the world's biotech companies, she says.

But on the first day of the meeting, several exhibitors and delegates commented that the turnout was not as good as it might have been. This could just be because there are several other big biotech-based meetings going on at the end of the year, says Alasdair Street, Business Development Manager at PharmaLinks, a Glasgow-based initiative set up to develop and promote research coming out of the Universities of Glasgow and Strathclyde.

Alternatively, say delegates, the poorly perceived turnout could reflect the cautious mood of an industry that has yet to deliver and is struggling to compete with the USA.

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