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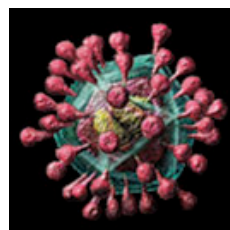
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WEB FOCUS

SARS

Is the SARS virus mutating?

Viruses such as HIV and those that cause influenza have often been described as 'wily' because they mutate rapidly, a trait that helps them to evade drugs or the human immune system. But so far, the SARS virus seems remarkably invariant: the genome sequences of 14 isolates from patients in Singapore, Toronto, China and Hong Kong have not revealed any changes of real consequence¹⁷.



This isn't because the SARS virus fails to mutate, but rather that the mutations thrown up so far haven't proved to be particularly beneficial to it. As the virus has so far encountered little resistance from its new human hosts, there has been little selective pressure to cause new mutants to be retained.

Coronaviruses are quite sloppy when it comes to replicating their genetic material, making one error for every 10,000 nucleotides they copy — roughly the same error rate as HIV. But coronaviruses have a trait that allows them to weed out mutations as they occur. Rather than relying on a single template genome, the enzyme responsible for copying the viruses' genetic material sometimes jumps around between multiple copies of the viral genome present in an infected cell. So each new genome is actually copied from several templates, reducing the chance that any given mutation will become entrenched in the viral population.

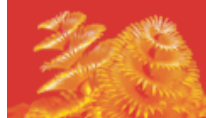
But if one of these jumps is imprecise, a whole chunk of genome can get skipped, resulting in the deletion of part of an important gene. The consequences can be dramatic, particularly if the change affects the protein spikes that bind to the surface of the viruses' cellular victims. For example, in 1984 a new respiratory ailment appeared on European pig farms. It turned out to be a deletion mutant of a coronavirus that previously had infected piglets' stomachs¹⁸. The altered spike protein had changed the type of cells the virus could enter. Although the new disease was not generally lethal, it has since spread worldwide and complicated diagnosis of the gut disease.

A genetic deletion may also have helped the SARS virus to make the transition from its animal reservoir to humans. But, if so, it is a different type of change — the spike protein remains intact. Instead, compared

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with the viral strains found in animals on sale in southern Chinese markets, the SARS virus lacks 29 nucleotides in the gene for a protein of unknown function, which is attached to the inside of the virus's protective coat.

Should SARS return to haunt us, it will probably not remain as stable as it has been so far, particularly if it is attacked with antiviral drugs. Our immune systems could force changes, too. "Once enough people develop immunity, mutations will be favoured, just as you see with flu viruses," predicts Michael Lai, a molecular virologist at the University of Southern California in Los Angeles.

Jonathan Knight

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Are drugs for SARS on the horizon?

From the moment the viral culprit behind SARS was unmasked, drug-discovery researchers leapt into action. So far, the main approach has been one of brute force: screening hundreds of thousands of compounds for their ability to attack lab cultures of the virus.

The US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, is coordinating a massive random screen of both licensed drugs and those still under development. This work has been contracted to the US Army Medical Research Institute of Infectious Diseases at Fort Detrick, also in Maryland, where more than 300,000 compounds — many of them supplied by pharmaceutical companies — have so far been tested on viral cultures grown in monkey kidney cell lines. "We've had lots of hits, and some are looking better than others," says Fort Detrick virologist Robert Baker.

A similar, but smaller initiative, based at the University of Frankfurt in Germany, has shown that a compound called glycyrrhizin, derived from liquorice roots, can rid monkey kidney cells of the SARS virus¹⁹. In work that has yet to be published, the Frankfurt team has confirmed the effectiveness of glycyrrhizin in a human cell line. Although relatively non-toxic and already licensed for use in conditions including hepatitis C, glycyrrhizin only works at very high doses. So the Frankfurt researchers, led by Prakash Chandra, are collaborating with medicinal chemists at the Russian Academy of Sciences' Institute of Organic Chemistry in Moscow, who have synthesized a series of related compounds²⁰. They hope that one of these will prove particularly effective against the SARS virus.

Other researchers are trying a more directed approach. Erik De Clercq of the Catholic University of Leuven in Belgium, for instance, is screening selected compounds from his large library of antiviral chemicals, many of which interfere with viral replication. "I believe that rational screening based on putative targets is likely to be more efficient than random screens," he says.

Rolf Hilgenfeld, a structural biologist at the University of Lübeck in Germany, meanwhile, has solved the structure of a key SARS enzyme called proteinase, which turns viral proteins into the active forms required for viral replication²¹. Using a computer model of this structure, his team has also begun to predict which drugs might inhibit the enzyme's activity. Hilgenfeld is now collaborating with a Chinese group led by

Jiang Hua-Liang of the Shanghai Institute of Materia Medica, which has the supercomputing power to expand upon this work.

But the difficult part will be moving into animal experiments and eventual human trials. So far, there is only one validated animal model for SARS, the cynomolgus macaque (*Macaca fascicularis*)⁸, which isn't ideally suited for large-scale investigations of candidate drugs. A good small-animal model is urgently needed, say researchers.

Alison Abbott

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What about a vaccine?

If SARS stages a comeback, the best tool for blunting its threat will be an effective vaccine. And the good news is that vaccines already exist for animal coronaviruses. "We can immediately apply this expertise to SARS," says virologist Peter Rottier of Utrecht University in the Netherlands, who is developing a vaccine against a coronavirus that kills cats. Another encouraging sign is that the condition of SARS patients seems to improve if they are given serum from previously infected people, which indicates that human antibodies can neutralize the virus.

Perhaps the easiest approach is to stimulate immunity using a killed SARS virus. "It's the first thing we'll try," says Rino Rappuoli of vaccine manufacturer Chiron in Siena, Italy. But relying on killed viruses is not ideal — in part because ensuring that all viruses in a vaccine are dead and yet retain the ability to stimulate the immune system is tricky.

The next option is a weakened SARS virus that can survive in humans long enough to challenge the immune system, but which doesn't cause disease. Such vaccines are normally made by culturing viruses in animal cell lines for generation after generation, selecting each time for the least potent offspring. They have the advantage that they can be made to infect cells in the respiratory tract — which may prove crucial to stopping SARS in its tracks. But safety remains an issue, as a weakened strain might mutate to become a lethal virus in its own right.

The best way around this, and the approach that Rottier has used to make a prototype cat coronavirus vaccine, is precisely targeted genetic modifications. Genes not needed for the virus's survival but required for it to cause disease are removed. All of the known coronaviruses, including the SARS virus, seem to have these genes in common, and knocking them out wholesale would make it almost impossible for the SARS virus to mutate back to a dangerous form. But there is still the chance that it could recombine with other coronaviruses to recover its lethal genetic machinery.

Other approaches avoid any possibility of a vaccine causing SARS. For instance, harmless viruses could be engineered to contain genetic sequences from the SARS virus. Such vaccines could again be made to infect cells in the respiratory tract, and the approach has been used successfully in animals — for instance in a prototype vaccine against a coronavirus that causes bronchitis in chickens²². A simpler and even safer alternative would be vaccines based on viral proteins that stimulate the immune system, but this approach has had only limited success against animal coronaviruses.

What works in animal diseases may not provide a perfect guide to developing a SARS vaccine, however. Experience has shown that individual coronaviruses can interact with their hosts in quite distinct ways. "The trick is finding a vaccine that pushes all the right immunological buttons," says Dave Cavanagh at the Institute for Animal Health at Compton in Berkshire, UK. Finding a candidate that achieves this against the SARS virus will require extensive studies in animals.

If all goes well, a SARS vaccine could reach the market in as little as four years, say experts. But there's a lot that could go wrong at any stage. So for the foreseeable future, health officials had better plan on tackling the disease without this key defensive weapon.

Tom Clarke

more SARS questions

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