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The complex issue of immune evasion

Henry Nicholls, BMN News

US researchers claim to have identified a novel molecular mechanism that enables HIV to escape detection by its human host.

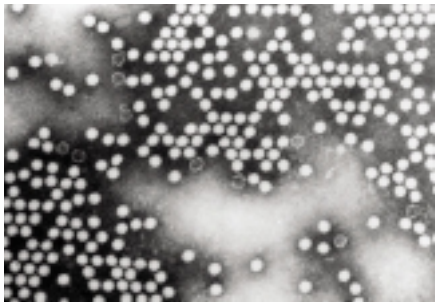
Nef-defective viruses

The findings relate to the HIV protein Nef. Patients with a rare strain of HIV that lacks this protein are known to take a long time to develop AIDS. 'Infection with Nef-defective viruses is typically associated with unusually low levels of viral replication and markedly slower rate of progression to AIDS,' said Jacek Skowronski of the Cold Spring Harbor Laboratory in New York State (http://www.cshl.org).

Skowronski and colleagues purified a major protein complex in the infected host that associates with Nef. Mass spectroscopy of this complex revealed its major subunits – two proteins called DOCK2 and ELMO1.

These binding proteins work together to modulate the activity of Rac enzymes, which are required for lymphocyte migration and antigen-specific responses, Skowronski's team reports in the January issue of *Public Library of Science Biology* [1]. This pattern of events prevents HIV-infected T cells from travelling to the lymphatic tissues where they could otherwise launch an immune attack on the viral infection, the researchers argue.

'The identification of DOCK2–ELMO1–Rac complex as the effector of Nef for signal transduction in T cells now opens a way to define the precise contribution and role(s) of this pathway for viral replication and progression to disease,' Skowronski told *BioMedNet News* (http://gateways.bmn.com/).



Scanning electron micrograph of HIV-1 budding from cultured lymphocyte. CDC/PHIL

Unanswered questions

Notably, their analysis appears to rule out the association of Nef with several other proteins that have been previously been implicated in the signalling pathway. 'This includes cellular proteins such as Vav, PAK, ... and others,' they write.

The discovery of this abundant Nef multi-protein complex is an exciting finding, says Oliver Fackler, a virologist at the University of Heidelberg in Germany (http://www.uni-heidelberg.de/). But, he cautions, many questions remain to be answered and it is too early to rule out a role for other proteins, notably Vav, that are not abundant in the complex.

Harry Kestler, a molecular geneticist who now works at Lorain County Community College in Ohio (http://www.lorainccc.edu/), was a member of the team that worked out that Nef is an important player in the invasion of the host immune system by HIV. Since his research on Nef in the 1980s, the picture is still far from clear, he says.

Laying the foundations

This latest research has merit and the results deserve to be followed up, says Kestler. However, the story presented by Skowronski and his colleagues seems almost too good to be true, he adds. 'I think drug houses would want to see a little more evidence that [the DOCK2–ELMO1–Rac complex] is the target of Nef.'

Nevertheless, understanding how Nef interacts with these proteins to spread infection could lay the foundation for new therapies aimed at inhibiting and arresting HIV infection. 'This effect of Nef provides another mechanism to suppress the antiviral immune response,' conclude Skowronski and colleagues.

Reference

1 Janardhan, A. *et al.* (2004) HIV-1 NefbBinds the DOCK2-ELMO1 complex to activate Rac and inhibit lymphocyte chemotaxis. *PLoS Biol.* 2, E6

1359-6446/04/$ – see front matter PII: S1359-6446(04)03035-1