Defying death: showing Bcl-2 the way home

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Bcl-2 and Bcl-x_L perform important functions in cell life or death decisions by setting the threshold for activation of the programmed cell death machinery. FKBP38, a member of the immunophilin family, has now been identified as a new Bcl-2/Bcl-x_L-binding partner. Furthermore, FKBP38 seems to be crucial in targeting Bcl-2/Bcl-x_L to the correct cellular locations.

Programmed cell death (apoptosis) is used to eliminate superfluous, aged, injured or infected cells in diverse biological settings[1]. During apoptosis, cells are dismantled from within and display plasma membrane alterations that attract the attention of phagocytic cells, thereby ensuring removal of the dying cell with the minimum of disturbance to its neighbours. A key event in many, if not all, instances of apoptosis is the activation of caspases, a family of cysteine proteases. Active caspases orchestrate apoptosis through limited proteolysis of approximately 500 cellular proteins[2]. A major pathway to caspase activation and

The Hitchhiker's Guide to HIV

The primary aim of HIV at initial infection of a cell is to rapidly deliver its RNA genome to the nucleus for integration into the host DNA. To get there, its large virion particles must first navigate through the cytoplasm towards the nuclear pore. But how does it get there before the cell is alerted to its presence? Hope and colleagues (McDonald, D. *et al. J. Cell Biol.*, **159**, 441–452 (2002)) have visualized the movement of individual HIV particles in live cells and find that in common with other subvertive viruses, HIV does this by 'hitchhiking a ride' with one of the cell's own motors, dynein.

To follow the HIV virions' movement, the authors fused green fluorescent protein (GFP) to one of the viral accessory proteins, Vpr. They then followed the movement of GFP-labelled virions through the cytoplasm of infected cells and showed that they move along a curvilinear path, showing significant association with the microtubule network, but not actin. To address the significance of this association, they looked at the consequences of disrupting the actin or microtubule networks for particle transport. Surprisingly, a complete block in particle transport occurred only when both the actin and microtubule networks were disrupted, suggesting that both are important for HIV movement.

The authors then went on to demonstrate unequivocally that the viral particles do track along microtubules (see figure). They used real-time imaging to track the movement of particles along fluorescently labelled tubulin, and they also showed using correlative electron microscopy (in which a cell is first imaged on a fluorescence microscope and then processed for electron microscopy), that single viral particles are attached to microtubules.

To investigate the functional significance of the microtubule association, they injected antibodies to disrupt the function of the microtubule motor, dynein. Importantly, they found that blocking dynein function alone prevented movement of particles away from the periphery of the nucleus.

So how do we resolve this essential role of dynein with the results of the drug treatments, which suggest that actin and microtubules function redundantly during HIV transport? Previous work has also suggested that both actin and microtubules are

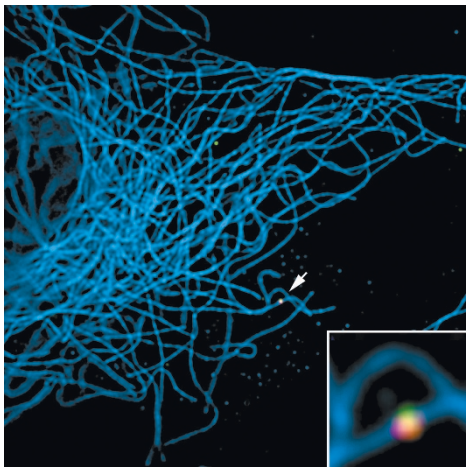

Figure 1 **Fluorescent microscopy image of an HIV reverse-transcription complex (RTC) on a microtubule (white arrow). Microtubules are shown in blue, incorporated fluorescent nucleotides in red and GFP–Vpr in green. A close-up image of the RTC is shown in the inset (lower right).**

important for HIV infectivity (*J. Exp. Med.*, **188**, 2113–2125, 1998). Therefore, the authors favour a model where actin is required for short-range movement of the HIV complexes at the periphery of the cell, and perhaps then to load particles onto microtubules, which mediate the long-range transport of particles towards the nucleus. It will be important to demonstrate association of the HIV particles with actin at the periphery to support this model. However, this idea is consistent with a growing list of crosstalk between the actin and microtubule networks and raises curiosity about the mechanism by which HIV may be transported along actin and then handed over to dynein for microtubule transport. Needless to say, these tantalizing first images of the path taken by HIV will spark further studies into these and other key questions.

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