In This Issue

The macrophage home of HIV

HIV assembles in a compartment that lies deep within macrophages yet is continuous with the extracellular environment, report Deneka et al. (page 329).

HIV forms membrane-encapsulated particles that assemble at, and bud off from, the surface of infected T cells. In macrophages, however, the majority of virus particles are found intracellularly and have been reported to associate with structures containing an endosomal marker called CD63.

Deneka and colleagues’ data, however, indicate that HIV does not enter macrophages by endocytosis. Upon HIV infection, the virus did not colocalize with any other endosome markers besides CD63. It instead associated with a newly identified vesicular structure marked by the transmembrane receptors CD81, CD9, and CD53.

The CD81/9/53 structures were shown by electron microscopy to be connected to the outside of the cell by narrow channels that are too small for HIV to pass through. By being essentially outside and inside at the same time, HIV would be simultaneously protected from the acidic digestive environment of endosomes and lysosomes and from the humoral immune system.

The authors propose that these structures might also allow for a rapid release of virus particles for their transmission to other cells. They are currently trying to determine the function of the CD81/9/53 compartments in uninfected macrophages.

In uninfected macrophages, endosomal CD63 did not colocalize with these CD81/9/53 compartments. So why does it accumulate there upon HIV infection? CD63 can be incorporated into the membrane capsule of HIV. The authors suggest that CD63 might normally traffic in small amounts throughout internal membranes and get swept up by HIV into CD81/9/53 structures.

Two other recent reports agree that HIV particles bud off from plasma membrane in macrophages rather than being associated with endosomes (Jouvenet et al. 2006. PLoS Biol. 4:e435; Welsch et al. 2007. PLoS Pathog. 3:e36). Now it is shown that this plasma membrane region is both intracellular and extracellular at the same time. JCB

Recruitment but no repair

A DNA repair protein turns up at the job site even without its tool kit, according to Uematsu et al. (page 219). Its visit is then prolonged by its inefficiency.

Fixing double strand breaks in DNA by nonhomologous end joining (NHEJ) requires a DNA-dependent protein kinase (DNA-PK) to bind to the loose ends of broken DNA and a ligase to do the gluing. This protein machinery must turn up and fix the ends rapidly to minimize the chance that DNA diffusion causes the wrong partners to be glued back together.

Very little is known, however, about the in vivo dynamics of NHEJ. Here, Uematsu et al. describe the dynamics of DNA–PK recruitment in vivo. DNA–PK is composed of two subunits: Ku70/80 and DNA–PKCS. They found that both subunits accumulated at damaged sites within two seconds after targeted DNA breakage. This repair site recruitment was dependent on the Ku70/80 subunit.

DNA–PKCS has a kinase domain and a cluster of phosphorylation sites, both of which are needed for mending DNA. Mutation of either, however, did not impair the enzyme’s recruitment speed.

Despite turning up for work as usual, the mutant repair proteins didn’t leave as quickly as the wild type. DNA–PKCS is well-known for performing autophosphorylation, and this ability is necessary for DNA repair. Since recruitment of the mutant proteins was normal but repair was deficient, the authors suggest that the main target of DNA–PKCS kinase activity is itself. Autophosphorylation might be the signal that the two loose DNA ends have come together. It most likely triggers the release of DNA–PK and allows access for the ligase to do its gluing. JCB

A repair protein (green) that lacks its kinase activity (left) or phosphorylation sites (right) still turns up at the repair site (blue).