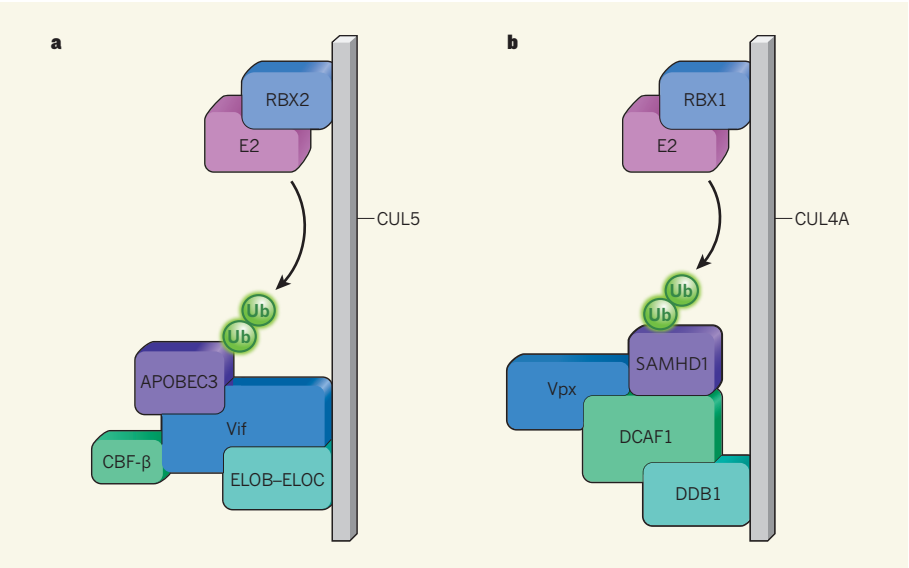

Figure 1 | Destruction of host-cell antiviral proteins. **a**, Guo and colleagues' crystal structure[2] shows the HIV-1 Vif protein occupying a central position as a substrate receptor in the CRL5 complex formed between host-cell proteins CBF-β, ELOB–ELOC, CUL5, an E2 enzyme and RBX2. The substrate, an APOBEC3 protein, is recruited by Vif and marked by ubiquitin molecules (Ub), which are transferred from E2 by RBX2. This tags the substrate for degradation by the cell. **b**, Schwefel *et al.*[3] show that the Vpx protein from sooty mangabey simian immunodeficiency virus occupies a comparatively peripheral position in the complex it forms with host-cell proteins. Vpx binds DCAF1 and recruits the substrate SAMHD1; DDB1 has an analogous role to ELOB–ELOC. The proteins interact with CUL4A, RBX1 and an E2 enzyme to form a CRL4A complex, and SAMHD1 is tagged for destruction by ubiquitination.

triphosphohydrolase that reduces the cellular levels of dNTPs (the substrates for DNA synthesis), thereby suppressing reverse transcription, especially in non-proliferating cells such as myeloid cells and resting T cells[4].

Vif and Vpx both work by directly recruiting their target restriction factors to host-cell cullin-RING ubiquitin ligases (CRLs), a diverse family of multicomponent enzymes that add ubiquitin chains to substrates[5], thereby marking them for destruction by the proteasome (a cellular protein-degrading machine). The CRLs are assembled with a cullin (CUL) protein (of which there are six in humans) as the central scaffold. Their catalytic core is built around the carboxy terminus of the CUL and also contains an RBX (or ROC) RING-finger protein and an associated E2 ubiquitin-conjugating enzyme (Fig. 1). The amino-terminal region is devoted to substrate recruitment: typically, the CUL binds a substrate adapter molecule, which in turn connects to a substrate receptor and its bound substrate. Now, Guo *et al.*[2] and Schwefel *et al.*[3] present the contrasting mechanisms used by Vif and Vpx to engage CRLs.

Previous attempts to resolve the structure of the Vif protein, either alone or in association with its CUL5-based CRL (CRL5) or APOBEC3 substrates, had been unsuccessful. A game-changing advance came with the discovery[6,7] that the transcription factor CBF-β is also required for the function of HIV-1 Vif. It rapidly emerged that Vif and CBF-β form a stable heterodimer, and this advance enabled the purification of enough soluble full-length Vif for structural studies.

Guo *et al.* (page 229) describe the first crystal structure of a complex comprising Vif–CBF-β, the ELOB–ELOC heterodimeric substrate adapter and an amino-terminal fragment of CUL5 (Fig. 1a). The structure shows that Vif occupies a crucial nucleating position within this pentameric complex, simultaneously interacting with CBF-β, CUL5 and ELOC, and promoting CRL assembly. By contrast, CBF-β contacts only Vif and seems to serve a chaperone-like function by helping Vif to fold into an active conformation. Interestingly, the contacts that Vif makes with ELOC (through an evolutionarily conserved peptide sequence called the BC box) and CUL5 imitate those made by the cellular protein SOCS2, a CRL substrate receptor involved in the downregulation of growth-hormone signalling. This suggests that the two proteins have adopted a similar mechanism for CRL5 recruitment. A fascinating future step would be to add APOBEC3 proteins to the complex; as discussed by the authors, the amino-acid residues in Vif that are required for engaging A3F or A3G are solvent accessible, and are therefore predicted to be available for direct interactions with these substrates.

Interest in Vpx intensified following the discovery that it provokes the degradation of SAMHD1 during the early stages of virus infection. HIV-2 and diverse simian immunodeficiency viruses (SIVs) encode Vpx or Vpr proteins with this function[8]. Interestingly, HIV-1 does not, raising important questions of whether and how it evades SAMHD1-mediated restriction. Building on earlier structural studies from their group[9], Schwefel *et al.* (page 234) now present the crystal structure of a complex between the Vpx-binding element of SAMHD1, the carboxy-terminal WD40 domain of the CRL4A substrate receptor DCAF1, and the Vpx protein of the SIV that infects sooty mangabeys (Fig. 1b). The structure shows that all three components contact each other, with extensive interactions between Vpx and DCAF1 creating a shared surface to which SAMHD1 binds. Although structures of Vpx-containing complexes with additional CRL components are eagerly anticipated, the authors proceeded to model a CRL–Vpx–SAMHD1 complex using previously determined structures. Satisfyingly, the model shows SAMHD1 positioned close to the RING domain of RBX1, a location that would be expected to render it receptive to ubiquitination.

Thus, these new reports show that although Vif and Vpx both manipulate CRLs to recognize host antiviral proteins and trigger their ubiquitination, they achieve this through contrasting mechanisms: Vif occupies a central organizing position and acts as a substrate receptor, whereas Vpx operates more peripherally to remodel the substrate receptor and facilitate substrate binding. These papers highlight not only the remarkable structural flexibility of assembled CRLs, but also the unrelenting capacity of viral proteins to commandeer cellular pathways for the benefit of the virus. Visualizing such structures and their underpinning protein interactions at atomic-level detail should inspire rational drug-design efforts aimed at interfering with fundamental aspects of CRL function. Pharmacological interventions that spare restriction factors from virus-induced elimination may offer a further therapeutic approach for treating HIV infections. ■

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CORRECTION

The News & Views article 'Cell biology: The beginning of the end' by Judith Campisi (*Nature* **505,** 35–36; 2014) omitted the name of the first author of ref. 5, Muñoz-Espín, in the final sentence of the first paragraph. The online versions of the article are correct.