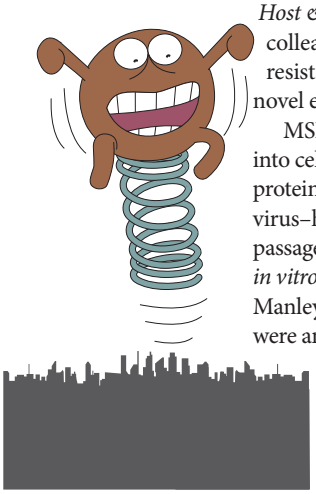
VIROLOGY

Unusual escape for HCMV



The clinical development of a neutralizing antibody to treat human cytomegalovirus (HCMV)-associated retinitis in patients with AIDS was stopped at the Phase II–III stage owing to a lack of efficacy. At the time, it was suspected that the virus had developed resistance to the antibody, MSL-109, but the mechanism involved was unclear. Writing in *Cell Host & Microbe*, Kate Manley and colleagues now suggest that this resistance can be explained by a novel escape mechanism.

MSL-109 blocks HCMV entry into cells by targeting envelope glycoprotein H (gH), which is required for virus–host cell fusion. By repeated passage of HCMV str. VR1814 *in vitro* in the presence of MSL-109, Manley *et al.* generated viruses that were antibody resistant (HCMV VR1814-MSL109R). Sequence analysis of all of the viral glycoproteins required for host cell entry, followed by analysis of the entire genomes of resistant viruses, identified no single change that was responsible for this resistance. Taken together with the fact that viral passage in the absence of MSL-109 led to the rapid reversal of resistance, this suggested that a non-genetic mechanism was involved.

The relationship between the development of resistance and antibody concentration was investigated, and resistance development was found to be dose dependent. Furthermore, the authors detected an immunoglobulin G heavy chain in the HCMV VR1814-MSL109R virions isolated from infected cell lysates, indicating that the antibody may be incorporated into the virion. Immunoprecipitation and colocalization analyses revealed that MSL-109 was selectively taken up by HCMV-infected cells and that MSL-109 and gH colocalized in viral assembly compartments. Further studies revealed that HCMV VR1814-MSL109R was defective for entry into non-fibroblast cells and that this tropism change could be reversed by removal of antibody. Moreover, it was found that the mechanism of entry into naive non-immune cells differed between wild-type and resistant virus, with the antibody-resistant virus entering cells by a pH- and clathrin-dependent mechanism that required the Fc domain of MSL-109.

The authors present a model in which HCMV escapes the neutralizing effect of MSL-109 by incorporating the Fc domain into assembling virions. Although the authors acknowledge that this mechanism of escape is likely to be rare, they caution that the mechanism involved should be fully investigated before further antibody therapies for HCMV infection are pursued.

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ORIGINAL RESEARCH PAPER Manley, K. *et al.* Human cytomegalovirus escapes a naturally occurring neutralizing antibody by incorporating it into assembling virions. *Cell Host Microbe* **10**, 197–209 (2011)