

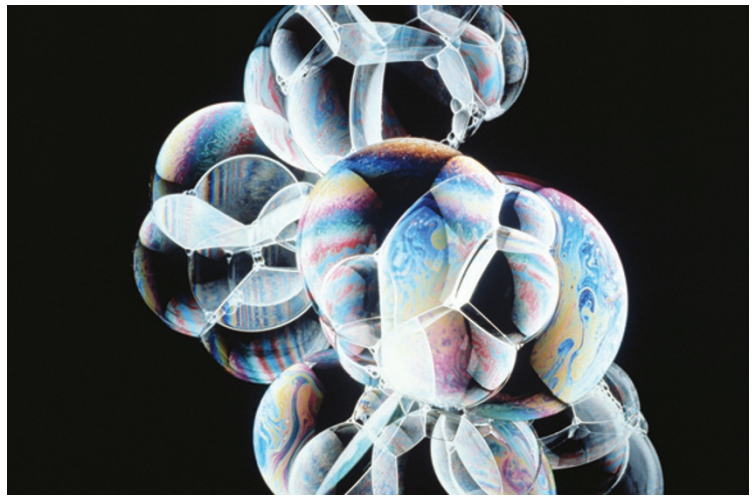
 VIRAL PATHOGENESIS

Death by viroporin

A paper recently published in *Cellular Microbiology* reports that viroporins of hepatitis C virus (HCV), poliovirus and other animal RNA viruses induce apoptosis in host cells.

Viroporins are present in tiny amounts in the virions of most enveloped animal RNA viruses. Examples include Sindbis virus 6K protein, influenza A virus M2 protein, poliovirus 2B and 3A proteins, mouse hepatitis virus E protein, HIV Vpu and severe acute respiratory syndrome coronavirus E protein. These small (around 100 amino acids), extremely hydrophobic proteins oligomerize to form pores in host-cell membranes through which viruses can bud. Viroporins contribute to the pathology of disease by altering membrane permeability and disrupting ion homeostasis in cells.

Inspection of the structural features and hydrophobicity profiles of small proteins encoded by HCV revealed two candidate viroporins, NS4A and p7. Using an expression system that was based on Sindbis virus to mimic the expression of viroporins during infection, the comparative effects of selected viroporins — Sindbis virus 6K protein, influenza A virus M2 protein, poliovirus 2B and 3A proteins, mouse hepatitis virus E protein and HCV p7 and NS4A proteins — on baby hamster kidney (BHK) cells was evaluated. On expression, each protein that was tested altered membrane permeability, which confirmed that these proteins are *bona fide* viroporins.



Mouse hepatitis virus E protein and HIV Vpu had both previously been shown to induce apoptosis, so Madan and colleagues looked for characteristic signatures of apoptosis in BHK cells that expressed viroporins. All the viroporins induced chromatin condensation, nuclear DNA fragmentation and activation of the key apoptosis enzyme caspase 3, but the strongest pro-apoptotic response was induced by HCV NS4A and poliovirus protein 2B.

Another intriguing link between viroporins and apoptosis is the reported association of a fraction of HCV p7 and NS4A proteins with mitochondria. The authors showed that HCV NS4A and poliovirus 2B colocalized with mitochondria and that expression of other viroporins altered mitochondrial morphology and distribution. Notably, the expression of all viroporins led to the release of cytochrome *c* from mitochondria.

Taken together, this evidence led the authors to propose that viroporins activate apoptosis by the mitochondrial pathway. These findings are all the more surprising given that poliovirus proteins 2B and 3A suppress apoptosis in HeLa cells at low levels. It is possible that viroporins have different effects depending on the level of expression and/or the host-cell type.

The induction of apoptosis in host cells by viruses is common and could aid virus spread. The next step in understanding the intriguing links between viroporins and apoptosis will be to unravel the mechanisms by which viroporins trigger apoptotic pathways and demonstrate that these findings are relevant during infection.

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ORIGINAL RESEARCH PAPER Madan, V., Castello, A. & Carrasco, L. Viroporins from RNA viruses induce caspase-dependent apoptosis. *Cell. Microbiol.* 25 Oct 2007 (doi 10.1111/j.1462-5822.2007.01057.x)