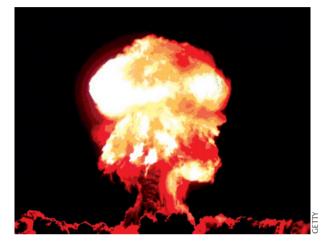
ANTIVIRAL IMMUNITY

Viral restriction goes nuclear

Promyelocytic leukaemia (PML) protein is the key organizer of nuclear bodies and has been implicated in defence against viral infection. Writing in the *Journal of Virology*, Maroui *et al.* now identify a specific nuclear PML isoform that functions in the host response to infection by sequestering the viral polymerase of an RNA virus that replicates in the cytoplasm.

PML-containing nuclear bodies are dynamic nuclear matrixassociated structures that harbour numerous transcriptional regulators. PML exists as seven different isoforms (I-VII) that differ in their carboxy-terminal regions as a result of alternative splicing. One isoform, PMLIV, has previously been shown to confer resistance to infection with rabies virus. Furthermore, cells derived from Pml- knockout mice are more sensitive to infection with encephalomyocarditis virus (EMCV); however the PML isoform (or isoforms) implicated in this antiviral defence, as well as their mechanism of action, remained unclear.

Maroui *et al.* stably expressed each of the seven PML isoforms in U373MG cells and, following a 12h infection of these cells with ECMV, found that only the presence of PMLIV led to undetectable levels



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of the viral proteins VP1, VP2 and VP3. Furthermore, the presence of PMLIV protected cells from EMCVinduced lysis, even at high multiplicity of infection, and it blocked viral RNA synthesis as determined by quantitative reverse transcription PCR. The PMLIVa variant, which lacks the region of the protein encoded by exon 5 but contains an identical C terminus, also blocked viral replication. The SUMOylation of PML at three sites is required for nuclear body formation and, accordingly, a PMLIV variant carrying a triple mutation of the SUMOylated lysines was not able to block viral replication.

So how does PMLIV block viral replication? The authors noticed that, although EMCV replicates in the cytoplasm, at early time points following infection of a cell the viral RNA-dependent RNA polymerase, 3Dpol, had a punctate distribution in the nucleus, suggesting a possible link with PML nuclear bodies. Using confocal microscopy, the authors observed that 3Dpol colocalized in the nucleus with PMLIV but not with other PML isoforms. Furthermore, through reciprocal coimmunoprecipitation assays, 3Dpol and PMLIV were found to interact with each other, and this interaction was lost in a PMLIV variant lacking the C-terminal region encoded by exons 8a and 8b. Importantly, specific depletion of PMLIV reduced the capacity of interferon to protect cells from EMCV infection. The authors suggest a model in which PMLIV acts as an antiviral mediator of interferon to prevent viral replication in the cytoplasm through sequestration of 3Dpol in nuclear bodies.

Several other PML isoforms have been linked with inhibitory effects against other DNA and RNA viruses, suggesting that nuclear bodies have an important role in the intrinsic host cell restriction of viral infection.

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ORIGINAL RESEARCH PAPER Maroui, M. A., Pampin, M. & Chelbi-Alix, M. K. PMLIV confers resistance to EMCV via the sequestration of 3D polymerase in nuclear bodies J. Virol. 12 Oct 2011 (doi:10.1128/IVI.05808-11)