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ANTIVIRAL IMMUNITY

Editing HLA-E expression

> HCMV infection ... results in miR-376a editing and, in turn, decreased HLA-E expression

In the first example of the regulation of HLA-E expression by microRNA (miRNA) editing, Mandelboim and colleagues report that infection with human cytomegalovirus (HCMV) induces a host RNA editing response that results in the downregulation of HLA-E expression and hence the increased natural killer (NK) cell-mediated killing of infected cells.

Adenosine deaminase acting on RNA (ADAR; also known as DRADA) enzymes catalyse RNA editing, which can change the specificity of miRNAs. There are two ADAR1 isoforms: ADAR1-p150 is known to be induced by interferons during viral infection, whereas the expression of ADAR1-p110 was previously thought to be constitutive. However, following infection of human foreskin fibroblasts (HFFs) with various HCMV strains (but not with other herpesviruses), ADAR1-p110 expression, but not that of ADAR1-p150, was markedly increased. Reporter gene expression from one of the three *ADAR1* promoters that control ADAR1-p110 expression was strongly induced as early as 6 hours after HCMV infection.

An increase in the level of miR-376a(e) — the edited form of miR-376a — was detected in HFFs following HCMV infection. Knockdown of *ADAR1* inhibited this HCMV-dependent increase in miR-376a editing, and overexpression of ADAR1-p110 resulted in increased levels of miR-376a(e). These results show that ADAR1-p110 is induced specifically during HCMV infection, leading to miR-376a editing.

The 3′ untranslated region (3′ UTR) of the gene encoding HLA-E was predicted to have two binding sites for miR-376a(e), but no binding sites for miR-376a. Overexpression of miR-376a(e), but not of miR-376a, in an HLA-E-expressing B cell line resulted in decreased HLA-E expression. In a reporter assay, mutation of either of the miR-376a(e)-binding sites in the 3′ UTR of the gene encoding HLA-E abolished miR-376a(e)-mediated repression of the reporter. So, miR-376a(e) directly binds this 3′ UTR, which inhibits the expression of HLA-E.

In HFFs transduced with an anti-miR-376a(e) sponge construct (which sequesters miR-376a(e)), HCMV infection resulted in increased HLA-E expression compared with control cells. The dependence of decreased HLA-E expression on ADAR1-p110 induction by HCMV in these cells was shown in knockdown experiments. In conclusion, HCMV infection induces ADAR1-p110 expression, which results in miR-376a editing and, in turn, decreased HLA-E expression.

To demonstrate the functional effect of this pathway, HFFs infected with HCMV were subject to killing by NK cells. Expression of the anti-miR-376a(e) sponge construct resulted in increased HLA-E expression and the inhibition of NK cell-mediated killing, whereas when HFFs were transduced with miR-376a(e) — leading to decreased HLA-E expression — killing of HCMV-infected cells was increased. This was presumably as a result of decreased inhibitory signalling through the HLA-E receptor CD94–NKG2A on NK cells.

It is unclear how this immune-stimulatory effect of HCMV fits with the well-known immune evasion properties of the virus. The authors suggest that HCMV may depend on RNA editing for successful gene expression and that the host has turned this dependence to its advantage. It is also possible that HCMV has evolved compensatory mechanisms to balance the ADAR1-p110-dependent antiviral response.

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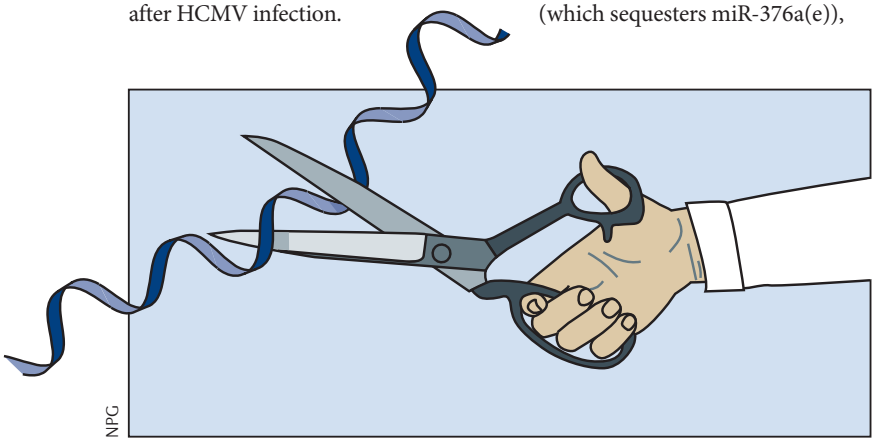

ORIGINAL RESEARCH PAPER Nachmani, D. *et al.* MicroRNA editing facilitates immune elimination of HCMV infected cells. *PLoS Pathog.* **10**, e1003963 (2014)