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HIV

FEZ blockade for HIV

Understanding how cells block viral replication can provide insights into host defence and viral multiplication. Several mammalian proteins that block retrovirus infection, including APOBEC3G, Zap, Fv1 and TRIM5 α , have already been identified. Now, research published in *Genes and Development* has shown that upregulation of FEZ1 (fasciculation and elongation protein ζ -1) can also prevent infection by retroviruses, including HIV-1.

The authors set out to identify new host alleles that mediate antiretroviral defence by mutagenizing rat fibroblast cells and selecting for resistance to Moloney murine leukaemia viruses (MLVs). The phenotypes of the different virus-resistant mutant cell lines that have been characterized reveal that the host might use different mechanisms in a multistep process to resist virus infection.

One mutant cell line, R3-2, which was 1,000-fold more resistant to MLV than the unmutagenized parental cells, was also resistant to HIV-1, and the block in virus replication was post-entry. Although reverse transcription of incoming viral RNA took place, new viral DNA was retained in the cytoplasm, instead of being transported into the nucleus to integrate into the cellular genome. Naghavi *et al.* used an array-based approach to probe the basis of retroviral resistance in R3-2 cells.

Comparison of transcripts from the parental and R3-2 cell lines

revealed a subset of genes that were differentially expressed in the mutant. This gene set was whittled down to seven candidate resistance alleles by selecting genes that were differentially expressed only in the R3-2 line and not in another mutant line resistant to MLV by a different mechanism.

Of the seven candidate alleles, *FEZ1*, which encodes a cytoskeletal transport protein that is the mammalian homologue of the *Caenorhabditis elegans* UNC-76 protein, was upregulated 30-fold in R3-2. The link between the transport function of FEZ1 and the block in MLV DNA transport to the nucleus in R3-2 cells was intriguing. The authors overexpressed FEZ1 in the parental cell line, which conferred resistance to MLV and HIV-1 without affecting the expression of any of the other six candidate resistance genes, indicating that FEZ1 overexpression alone can mediate retroviral resistance.

Depleting overexpressed *FEZ1* transcripts by RNA interference removed the block to virus infection. Finally, overexpressing rat *FEZ1* in human cells also blocked HIV-1 infection, so this seems to provide broad resistance to retroviral replication.

FEZ1 is a cytoskeletal transport protein. It is therefore plausible that altered abundance of this protein hinders the transport of viral DNA from the cytoplasm into the nucleus. This might be a general mechanism of resistance to any virus that relocates its genome to the nucleus during its replication cycle. The challenge now is to understand how *FEZ1* functions and how it might be upregulated *in vivo* to promote viral resistance.

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References and links

ORIGINAL RESEARCH PAPER Naghavi, M. H., Hatzioannou, T., Gao, G. & Goff, S. P. Overexpression of fasciculation and elongation protein ζ -1 (FEZ1) induces a post-entry block to retroviruses in cultured cells. *Genes Dev.* **19**, 1105–1115 (2005)