

 CELLULAR DEFENCE

Human cells clear foreign DNA

Foreign DNA poses a security threat to cells — for example, by allowing pathogen proteins to be expressed or by disrupting the genome. A mechanism by which human cells clear foreign DNA has now been identified — the first time that a DNA restriction system analogous to that of bacteria has been demonstrated in eukaryotes. This discovery has implications for a range of widely used technologies that involve the introduction of exogenous DNA into cells.

Human cells have several ways of responding to foreign DNA, many of which are triggered by the induction of interferons. However, little is known about how foreign DNA might be cleared from cells. The apolipoprotein B mRNA-editing complex 3 (APOBEC3) proteins have established roles in innate immune responses and are DNA cytidine deaminases — features that led Stenglein and colleagues to investigate the APOBEC3 family as potential mediators of foreign DNA clearance.

Phagocytes are particularly likely to encounter foreign DNA given their role in ingesting pathogens and cell debris. The authors showed that one APOBEC3 protein, APOBEC3A, is mainly expressed in a subset of phagocytic cells and is induced more than 100-fold in response to interferons. Furthermore, APOBEC3A expression has a negative effect on the integrity and stability of foreign DNA: it both reduces the efficiency of gene transfer using a chromosomally integrating plasmid and inhibits the transient expression of a reporter gene. Stenglein and colleagues showed that APOBEC3A deaminates foreign DNA, creating uracils that are substrates for excision by uracil DNA glycosylase 2 (UNG2), which leads to DNA degradation. By contrast, endogenous genomic DNA seems to be protected from the effects of APOBEC3A.

Stenglein and colleagues also showed that several other APOBEC3 proteins can clear foreign DNA in a range of cell types. As related proteins are present in all other vertebrates

examined, these findings suggest that the restriction of foreign DNA by deamination and degradation may be a widespread phenomenon. This work has implications for a range of technologies — from cell transfection to gene therapy and DNA vaccines — in which the clearance of exogenous DNA might present a substantial barrier to success.

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ORIGINAL RESEARCH PAPER Stenglein, M. D., Burns, M. B., Li, M., Lengyel, J. & Harris, R.S. APOBEC3 proteins mediate the clearance of foreign DNA from human cells. *Nature Struct. Mol. Biol.* 10 Jan 2010 (doi:10.1038/nsmb.1744)



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