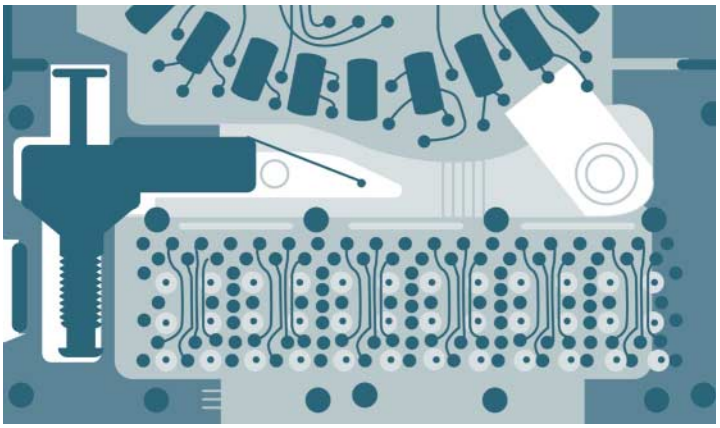
VIRAL IMMUNITY

New mechanism for APOBEC3G?



Members of the APOBEC protein family all contain consensus cytidine-deaminase motifs, some of which have been shown to catalyse the deamination of cytidine to uridine in DNA or RNA. Replication over the mutated uridine (which is recognized as thymidine by the polymerase machinery) then results in a guanosine (G) to adenosine (A) mutation in the pairing strand. APOBEC3G has potent anti-retroviral activity, and consistent with its proposed role as a cytidine deaminase, it induces high levels of deleterious G to A mutations in HIV-1 cDNA. Given that APOBEC3G has two consensus cytidine-deaminase motifs, one at each terminus, Sheehy and colleagues set out to find which of these is important for the antiviral effect.

First, they tested the ability of each domain to mutate DNA in an *in vitro* assay in which mutation of the RNA polymerase B gene of *Escherichia coli* by APOBEC3G is measured by the frequency of acquired resistance to rifampicin. Mutations in the amino (N)-terminal domain of APOBEC3G did not affect the frequency of rifampicin resistance, whereas mutations in the carboxyl (C)-terminus markedly decreased the frequency of resistant bacterial colonies. Surprisingly, this indicates that only the C-terminal cytidine-deaminase motif of APOBEC3G has DNA-mutating activity.

However, although mutations at the C-terminus inhibited the mutational activity of APOBEC3G, they did not significantly affect antiviral activity against susceptible strains of HIV-1. Comparison of the different APOBEC3G mutants showed that antiviral activity depends on at least one of the domains being intact, but it doesn't matter which one. It therefore seems that there might be an alternative mechanism, independent of DNA deamination, for the antiviral activity of APOBEC3G. Consistent with this, HIV-1 cDNAs recovered from cells infected with APOBEC3G-susceptible virions produced in the presence of C-terminal-mutated APOBEC3G showed no evidence of G to A hypermutation, despite the presence of a strong antiretroviral effect.

The authors experimentally ruled out a dominant-negative effect of C-terminal mutations on any DNA-mutating activity of the N-terminus of APOBEC3G. They also showed that the failure of C-terminal APOBEC3G mutants to edit viral cDNA did not result from a lack of virion packaging. Therefore, these results call into question the previously assumed absolute correlation between cytidine-deaminase activity and antiretroviral function of APOBEC3G, which might have implications for the function of other members of the APOBEC family.

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References and links

ORIGINAL RESEARCH PAPER Newman, E. N. C. *et al*. Antiviral function of APOBEC3G can be dissociated from cytidine deaminase activity. *Curr. Biol.* **15**, 166–170 (2005).

IN BRIEF

AUTOIMMUNITY

TLR ligands are not sufficient to break cross-tolerance to self-antigens.

Hamilton-Williams, E. E. *et al*. *J. Immunol.* **174**, 1159–1163 (2005).

The presence of autoreactive T cells in individuals who do not have autoimmune disease shows that this is not sufficient for the induction of pathology. This paper looked at the potential role of Toll-like receptor (TLR) ligation in providing non-specific inflammatory signals that are required to turn potential autoreactivity into overt disease. Transgenic mice expressing ovalbumin in pancreatic β-cells under control of the rat insulin promoter (RIP-mOVA mice) do not develop diabetes when injected with OVA-specific $CD8^+$ T (OT-I) cells in the absence of specific $CD4^+$ T-cell help, owing to T-cell deletion by cross-tolerizing dendritic cells (DCs). When these mice were also injected with ligands for TLR2, TLR3, TLR4 or TLR9, which could activate the DCs for cross-priming, the OT-I cells were still deleted unless OVA-specific $CD4^+$ T (OT-II) cells were added. Therefore, TLR ligation alone is not sufficient to break tolerance in this model, which is supported by the fact that infection with TLR-ligand-bearing pathogens does not commonly result in autoimmunity. This is in contrast to a recent study in *Nature Medicine* by Lang *et al.* (**11**, 138–145 (2005); covered as a highlight in the February issue of *Nature Reviews Immunology*), which showed that TLR ligation could convert the presence of autoreactive T cells into autoimmune disease in another transgenic mouse model of diabetes, through upregulation of MHC class I expression on the target organ by interferon-α produced in response to TLR stimulation. The difference between these studies could relate to the requirement for $CD4^+$ T-cell help to prevent deletion of $CD8^+$ T cells in the former model but not in the latter.

REGULATORY T CELLS

Contact-mediated suppression by $CD4^+CD25^+$ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism.

Gondek, D. C. *et al*. *J. Immunol.* **174**, 1783–1786 (2005).

The *in vitro* suppressive function of $CD4^+CD25^+$ regulatory T (T_{Reg}) cells is contact dependent, and cross-linking of glucocorticoid-induced tumour-necrosis factor (TNF)-receptor-related protein (GITR) on T_{Reg} cells abrogates this. Using DNA-microarray analysis, Gondek *et al.* showed that stimulation of T_{Reg} cells solely through the T-cell receptor increased levels of granzyme B cDNA but that concomitant GITR signalling markedly diminished such upregulation. Functionally, T_{Reg} cells isolated from granzyme-B-deficient mice were impaired in their ability to suppress *in vitro* $CD4^+CD25^-$ T-cell proliferation. However, the suppressive function of T_{Reg} cells was perforin independent, so the mechanism by which granzyme B affects T_{Reg}-cell-mediated suppression remains unclear. Interestingly, T_{Reg} cells induced $CD4^+CD25^-$ T-cell apoptosis, so further studies will aim to define the molecular link between T_{Reg}-cell production of granzyme B and $CD4^+CD25^-$ T-cell apoptosis.