IMMUNOLOGICAL MEMORY

How T cells survive

Much as plants compete for essential resources such as space, sunlight, water and nutrients, so peripheral T cells compete for limited growth and survival signals, which keeps the overall population size remarkably constant. The factors that regulate the size of the memory $CD4^+$ T-cell pool have long been a mystery, but a new study shows that the answer was under our noses all along.

Different T-cell subsets depend on distinct survival signals and, in this way, competition for the same 'niche' is avoided. Interleukin-7 (IL-7) and contact with MHC class I or MHC class II molecules are thought to maintain the naive $CD8^+$ and $CD4^+$ T-cell pools, whereas memory $CD8^+$ T cells require IL-7 and IL-15. But none of these factors seems to be required for the survival of memory $CD4^+$ T cells. Benedict Seddon and colleagues decided to revisit this issue.

First, the role of T-cell receptor (TCR) signals was investigated using mice deficient in both Lck and Fyn (crucial components of TCR signalling) that carried an inducible *Lck* transgene. When *Lck* was switched on, normal memory and naive T-cell compartments were generated. When the transgene was switched off, the naive $CD4^+$ T cells disappeared, but the memory-phenotype $CD4^+$ T cells survived, confirming previous reports that TCR signals are not required for the survival of memory T cells.

Previous studies have also ruled out a requirement for IL-7. But, what happens when both IL-7 and TCR signals are lacking? Lck-deficient memory $CD4^+$ T cells were transferred to lymphocyte deficient $Il7^{-/-}Rag1^{-/-}$ mice. The transferred cells failed to divide and few were recovered compared with similar transfers to $Il7^{+/+}Rag1^{-/-}$ mice. This

ANTIVIRAL IMMUNITY

Dengue's deadly second sting

Acquired immunity tends to mean that secondary virus infections are much less severe than the first infection. An exception is secondary infection with dengue virus, which is associated with the deadly dengue haemorrhagic fever (DHF). Why the second hit should be worse that the first is a mystery. One hypothesis is that DHF might be caused by the overproduction of cytokines by virus-specific T cells — but we know almost nothing about T-cell responses to the virus. Now, researchers in the UK and in Thailand have developed dengue-virus-specific MHC class I tetramers, which give the first insights into the virus-specific T-cell responses and their possible role in DHF.

Mongkolsapaya *et al.* identified a new dengue virus T-cell epitope presented by an MHC class I molecule that is prevalent in South East Asian populations (HLA-A*11). From this, they generated HLA-A*11–epitope tetramers and used them to track dengue-virus-specific $CD8^+$ T cells in Thai patients with secondary dengue-virus infection. Early in infection, they found that the epitope-specific T cells were present in low numbers and could not produce the antiviral cytokine interferon-γ (IFN-γ) — a state the authors refer to as "stunned". But, at later stages, the number of specific T cells increased markedly, peaking at 2 weeks, and they acquired the capacity to secrete IFN-γ. Notably, the patients with the most severe DHF had the highest peak levels of specific T cells (more than 2% of peripheral blood T cells).

Why are the numbers of virus-specific T cells initially so low? Although the epitope-specific T cells in the blood seemed to be proliferating vigorously during acute infection, further investigation indicated that most were apoptotic. So, activation-induced cell death might account for the lack of antigen-specific T cells during the crucial early stages of infection.

But the most intriguing finding of this study concerns the serotype specificity of the T cells. There are four dengue-virus serotypes, and tetramers were made with epitope variants representative of each

shows that both IL-7 and TCR signals are involved in the maintenance of the memory T-cell pool, but when either signal is missing, the other can compensate.

Further adoptive-transfer experiments showed that whereas IL-7 promoted both proliferation and cell survival, TCR signals mainly stimulated proliferation; experiments in intact mice confirmed that this holds true in the steady state.

So, in contrast to earlier assumptions, the homeostasis of memory and naive $CD4^+$ T cells is controlled by the same factors — IL-7 and TCR signals.

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References and links

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WEB SITE

Rose Zamoyska's lab: http://www.nimr.mrc.ac.uk/molimm/zamoyska/Welcome.htm

serotype. In many cases of secondary infection, a large number of T cells reacted preferentially with tetramers of a serotype that was different to that of the current infection. This hints that populations of memory T cells that are specific for a primary dengue-virus infection might be preferentially expanded and activated in a subsequent infection with a different serotype. The potential problem lies in the fact that the reactivated memory cells probably have a lower affinity for the secondary virus and will be less effective at controlling it. So, a dengue-virus vaccine might have to induce immunity to all four serotypes if it is to prevent DHF.

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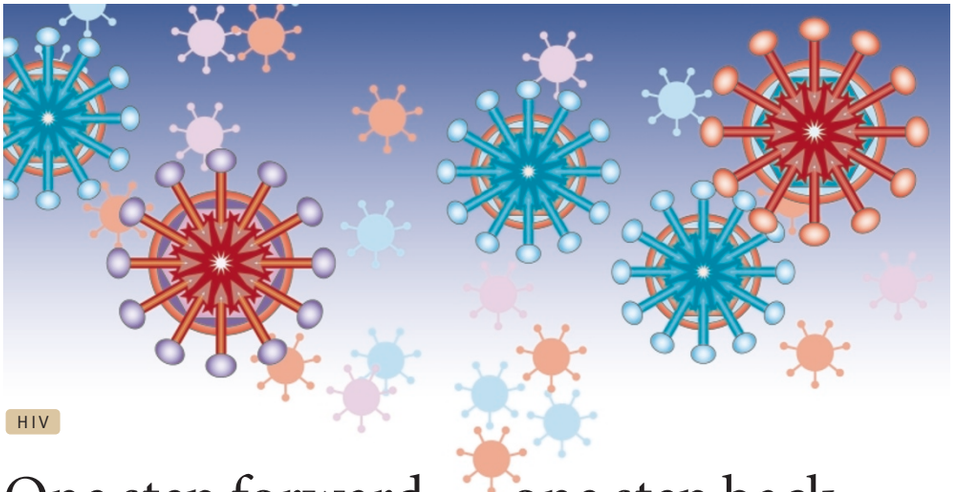
World Health Organization fact sheet on dengue and dengue haemorrhagic fever: http://www.who.int/inf-fs/en/fact117.html



HIV

One step forward … one step back

HIV is unable to multiply in certain human cells unless it expresses a protein known as virion infectivity factor (Vif). Although Vif was identified in the mid 1980s, it was only last year that a function for this protein was identified when an unequivocal correlation was observed between production of the cellular protein APOBEC3G (also known as CEM15) and the failure of Vif-deficient HIV-1 particles to produce infectious progeny in some host cells. Building on this breakthrough, four papers have just been published that further our understanding of the role of APOBEC3G as an endogenous viral inhibitor and the importance of Vif in overcoming this antiviral strategy.

APOBEC3G is a member of a family of cytidine deaminases that edit RNA, and recent studies have shown that certain members of this family target single-stranded DNA. These observations led several laboratories to hypothesize independently that APOBEC3G could block retroviral infectivity by deaminating cytosine in either virus RNA or DNA, so inducing mutation and/or instability of the virus genome. To address the question of whether APOBEC3G acted on RNA or DNA, Hui Zhang and colleagues sequenced newly transcribed genomic RNA from Vif-defective HIV-1 virions and found no significant mutations, indicating that RNA is not deaminated by APOBEC3G. They went on to investigate whether newly synthesized HIV-1 DNA was a substrate, and found guanine (G) to adenine (A) substitutions in all sequences that were analysed. Denise Lecossier and colleagues carried out a similar analysis on newly reverse transcribed HIV-1 genes *Env* and *U5* from infected cells. They also observed that G to A changes occurred more often in Vif-defective virions than in DNA from wild-type virions. Furthermore, no differences were observed in the frequency of G to A changes in virus DNA that was synthesized by wild-type and Vif-defective viruses produced in permissive cells — that is, cells in which the Vif protein is not required for propagative infection. The study by Lecossier and co-workers also showed that when Vif-defective virions produced in cells that lack APOBEC3G subsequently infected cells expressing this enzyme, their DNA was not edited, indicating that APOBEC3G has to be present in the virus particle to exert its effect.

In an article published simultaneously with the paper of Zhang and co-workers, Bastien Mangeat *et al.* showed that APOBEC3G was fully active on retrovirus particles that were only distantly related to HIV-1 — APOBEC3G is, therefore, a broadly active anti-retroviral that can both inhibit a wide range of retroviruses and compromise the expression from different pro-viruses. Using a different approach based on mouse leukaemia virus (MLV), Reuben Harris and colleagues also proved that APOBEC3G is a DNA deaminase that is packaged into virions during virus production, culminating in marked deamination of deoxycytidine in the retrovirus minus-strand complementary DNA. Using this system, they showed that MLV produced in cells expressing APOBEC3G had diminished infectivity that correlated with the introduction of a high number of G to A substitutions. These workers also showed that the Vif protein of HIV-1 could protect MLV from APOBEC3G-dependent restriction.

The bottom line from each of these investigations is that when HIV-1 replicates in cells that express APOBEC3G, the Vif protein, through mechanisms that are yet to be defined, can prevent the accumulation of defects in virus proteins that would otherwise result in a non-functional life cycle. The finding that APOBEC3G can act on a broad range of retroviruses, in addition to HIV-1, indicates that hypermutation generated by DNA deamination is a general innate defence mechanism against this important group of pathogens. It can also be argued that the accumulation of APOBEC3G-mediated non-lethal mutations in the replicating virus genome could make a crucial contribution to the variation of virus sequence that is observed in lentivirus populations.

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