

IN THE NEWS

Monkey vaccines

A vaccine has been developed that protects monkeys from Ebola and Marburg viruses, as reported in *Nature Medicine*. The breakthrough comes at a time when both viruses are on the rampage in Africa and are considered to be potential agents of bioterrorism.

Ebola and Marburg are closely related viruses that cause haemorrhagic fever — massive internal and external bleeding — and are lethal in up to 90% of infected monkeys and humans.

The authors of the recent report generated a replication-competent vaccine based on attenuated vesicular stomatitis virus (VSV) vectors expressing a glycoprotein from Ebola or Marburg virus. A single intramuscular injection of monkeys induced protective immune responses — both cellular and humoral — against lethal challenges with either virus.

As the authors report, the use of VSV vectors is “particularly attractive because they can be mucosally administered ... [and] ... VSV infections in humans occur fairly rarely” (*Nature Medicine*). Moreover, the live vaccine replicates in the recipient for a short time, generating a rapid and strong immune response. Although these are important features, the authors admit that there are still “questions regarding the safety of live attenuated vectors”, owing to their potential ability to recombine with other viruses (*New Scientist*).

Because monkeys suffer almost identical disease to humans, Steven Jones, the primary author of the study, said that “if we can protect them [monkeys] using this vaccine ... then this gives us a good deal of confidence that this will work in humans.” (*Reuters*). However, “it will be some time before we can use these vaccines in the field, but it is satisfying to know we are getting closer”, said one of Jones’s co-authors, Heinz Feldmann (*The Guardian*).

Lucy Bird

IMMUNOLOGICAL SYNAPSES



Visualizing T-cell fate: tolerance or priming

Whether the characteristics of a dendritic cell (DC)–CD4⁺ T-cell interaction determine whether the CD4⁺ T cell is primed or tolerized remains an open question. However, new insight into this is provided by two groups who have shown *in situ* that there are only subtle differences in the behaviour of CD4⁺ T cells after antigen encounter under conditions that result in priming or tolerization.

Previous two-photon microscopy studies that visualized T cells interacting with antigen-loaded DCs *in situ* indicated that, under priming conditions, antigen-specific T cells form stable contacts with DCs, whereas under tolerizing conditions, these stable contacts do not form. This has led to the hypothesis that the stability of the DC–T-cell interaction determines whether T cells are tolerized or primed. Because this hypothesis remains controversial, both groups set out to visually compare CD4⁺ T-cell priming and tolerance induction *in situ*.

To deliver antigen to DCs *in vivo*, Shakhar *et al.* used a fusion protein consisting of a DC-specific antibody fused to the ovalbumin (OVA) peptide that is recognized by T cells expressing the OT-II T-cell receptor (TCR). Antigen was delivered alone or in combination with a CD40-specific antibody to create tolerizing or priming conditions, respectively. T cells expressing both the OT-II TCR and enhanced green fluorescent protein (EGFP) were transferred to the immunized animals, and the behaviour of the cells in the lymph nodes was tracked intravitaly. Enhanced cyan fluorescent protein (ECFP)-expressing, antigen non-specific CD4⁺ T cells were co-transferred with the EGFP⁺OT-II TCR⁺ T cells to distinguish antigen-specific and non-specific behaviour. During the first 6 hours of imaging, under both tolerizing and priming conditions, EGFP⁺OT-II TCR⁺ T cells moved more slowly than the antigen non-specific ECFP⁺CD4⁺ T cells. In addition, a large proportion of the EGFP⁺OT-II TCR⁺ T cells were immobile, spending more time arrested than the control ECFP⁺CD4⁺ T cells. The only differences between tolerizing and priming conditions were observed between 6 and 12 hours, when the EGFP⁺OT-II TCR⁺ T cells regained speed more quickly under tolerizing conditions. Subsequently, between 12 and 18 hours, there was again little difference in the speed of the cells and in the amount of time spent arrested between EGFP⁺OT-II TCR⁺ T cells and control ECFP⁺CD4⁺ T cells under either tolerizing or priming conditions.

By contrast, Zinselmeyer *et al.* induced priming or tolerance by oral administration of OVA in the presence or absence of cholera-toxin adjuvant, and they imaged mucosal and systemic lymph



nodes both *ex vivo* and intravitaly. In these studies, mice had previously been administered CFSE (5,6-carboxyfluorescein diacetate succinimidyl ester)-labelled CD4⁺ T cells expressing the OVA-peptide-specific DO11.10 TCR. Similar to the observations of Shakhar *et al.*, under both tolerizing and priming conditions, DO11.10 TCR⁺ cells slowed down, formed clusters and appeared to stop. Further analysis indicated that the only differences were subtle: there were fewer T cells in each cluster under tolerizing conditions than under priming conditions, although the proportion of T cells entering clusters was greater under tolerizing conditions (particularly 20 hours after antigen feeding); also, at 20 hours after antigen feeding, the size of the clusters was greater under priming conditions.

These reports indicate that there are no marked differences in the initial phases of DC–CD4⁺ T-cell interactions that lead to the distinct outcomes of tolerance and priming. Indeed, stable interactions of antigen-specific T cells with DCs (which are thought to be the *in vivo* counterparts of immunological synapses) were correlated with activation and proliferation but not with tolerance or priming. However, further work will be required to determine whether the subtle differences that were observed in these studies are responsible for determining tolerance versus priming, as suggested by Zinselmeyer *et al.*, or whether events at time points later than those studied in these reports control this commitment step, as suggested by Shakhar *et al.*

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References and links

ORIGINAL RESEARCH PAPERS Shakhar, G. *et al.* Stable T cell–dendritic cell interactions precede the development of both tolerance and immunity *in vivo*. *Nature Immunol.* **6**, 707–714 (2005) | Zinselmeyer, B. H. *et al.* *In situ* characterization of CD4⁺ T cell behavior in mucosal and systemic lymphoid tissues during the induction of oral priming and tolerance. *J. Exp. Med.* **201**, 1815–1823 (2005)