

On the role of antigen persistence for CD4⁺ T cell responses

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In order to study how T cell responses are regulated by antigen persistence *in vivo*, we established a new double-transgenic mouse line that expresses a doxycycline (dox) -inducible I-E^k-restricted T cell epitope derived from moth cytochrome c (MCC) controlled by MHC class II and invariant chain regulatory sequences. Expression of the MCC epitope in the spleen was predominantly found in CD11c⁺ dendritic cells and could be titrated by dox over a three-log range. Transferred CFSE-labeled AND T cells proliferated vigorously, also strictly depending on dox.

We asked what impact antigen persistence has on the course of a CD4⁺ T cell response. We found that each division in the expansion phase depends on the presence of antigen *in vivo*, questioning whether CD4⁺ T cells ever proliferate "on autopilot." We now show that their incomplete expansion due to transient antigen exposure leads to deletion. In contrast, cells exposed to antigen throughout the expansion phase exhibit a very different gene expression profile early on and later differentiate into memory cells. Interestingly, DC activation by a stimulatory anti-CD40 mAb extends the half-life of I-E^k/MCC complexes *in vivo*. Therefore, our data demonstrate that prolonged antigen presentation, in addition to more costimulation, is an important component of DC activation for CD4⁺ T cell responses.

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