Nature Reviews Immunology | AOP, published online 1 February 2013; doi:10.1038/nri3400

T CELLS

The plastic virtues of a CD4$^+$ T cell

The mutually exclusive transcription factors RUNX3 and THPOK (also known as ZBTB7B) underlie the stability of the CD8$^+$ and CD4$^+$ T cell lineages, respectively. Now, two studies implicate these master regulators in the regulation of an unexpected degree of effector CD4$^+$ T cell plasticity in the gut.

> an unexpected degree of effector CD4$^+$ T cell plasticity in the gut

Mucida *et al.* and Reis *et al.* characterized an intestinal population of effector CD4$^+$ T cells that co-express CD8α. Notably, these cells lacked expression of the CD4$^+$ T cell lineage master regulator THPOK, expressed several cytotoxic T lymphocyte (CTL) markers (including granzyme B) and exhibited cytolytic activity *in vitro*. Moreover, Reis *et al.* observed expression of RUNX3 in these intestinal CD4$^+$CD8α$^+$ CTLs.

GETTY

Fate-mapping and adoptive-transfer experiments by Mucida *et al.* further showed that CD4$^+$ CTLs originate from THPOK$^+$ naive CD4$^+$ T cells. In addition, Reis *et al.* found transforming growth factor-β (TGFβ) and retinoic acid to be involved in the differentiation of naive CD4$^+$ T cells into THPOK$^-$RUNX3$^+$CD4$^+$CD8α$^+$ CTLs in the gut. Furthermore, Mucida *et al.* observed that CD4$^+$CD8α$^+$ CTLs are absent from the intestines of germ-free mice and of mice monocolonized with segmented filamentous bacteria, but appear in the intestines following reconstitution with specific non-pathogenic microorganisms. In agreement with previous reports, OT-II CD4$^+$CD8α$^+$ CTLs (which are specific for an ovalbumin epitope presented by MHC class II molecules) appeared in the gut following continuous oral administration of ovalbumin. Thus, continuous antigen stimulation in the presence of intestinal factors such as TGFβ and retinoic acid promotes the differentiation of CD4$^+$CD8α$^+$ CTLs.

So, what molecular events are involved in this differentiation process? Mucida *et al.* showed that antigen-induced reactivation of the *Thpok* silencer promoted the downregulation of THPOK expression and the subsequent derepression of *Cd8a* and other CTL-associated genes in effector CD4$^+$ T cells. In addition, Reis *et al.* observed that RUNX3 promotes the downregulation of THPOK, as RUNX3-deficient CD4$^+$ T cells largely failed to differentiate into THPOK$^-$CD4$^+$CD8α$^+$ CTLs.

Finally, Reis *et al.* asserted the functional capacity of CD4$^+$CD8α$^+$ CTLs by transferring control or genetically modified CD4$^+$ T cells into lymphopenic mice to induce colitis. Conditional deletion of *Thpok* in mature CD4$^+$ T cells prior to their transfer enhanced the differentiation of CD4$^+$CD8α$^+$ CTLs in the gut of the recipients, which then developed reduced intestinal inflammation compared with controls. By contrast, the transfer of RUNX3-deficient CD4$^+$ T cells led to exacerbated intestinal inflammation and also provided recipient mice with increased protection against infection with the enteropathogenic bacterium *Citrobacter rodentium*. This increased inflammatory potential was not associated with enhanced homing of RUNX3-deficient CD4$^+$ T cells to the gut following transfer but rather with the skewing of the gut-homing effector CD4$^+$ T cells from CD4$^+$CD8α$^+$ CTLs to T helper 17 (T_H17) cells. Thus, CD4$^+$CD8α$^+$ CTLs seem to have a quiescent phenotype *in vivo*. However, Mucida *et al.* report that MHC class II-dependent antigenic stimulation in the presence of interleukin-15 promoted a pathogenic function of CD4$^+$ CTLs *in vitro*, indicating an extreme plasticity for effector CD4$^+$ T cells in the gut.

Maria Papatriantafyllou

ORIGINAL RESEARCH PAPERS Mucida, D. *et al.* Transcriptional reprogramming of mature CD4$^+$ helper T cells generates distinct MHC class II-restricted cytotoxic T lymphocytes. *Nature Immunol.* 20 Jan 2013 (doi:10.1038/ni.2523) | Reis, B. S. *et al.* Mutual expression of the transcription factors Runx3 and ThPOK regulates intestinal CD4$^+$ T cell immunity. *Nature Immunol.* 20 Jan 2013 (doi:10.1038/ni.2518)