Nature Reviews Immunology | AOP, published online 7 April 2015; doi:10.1038/nri3849

REGULATORY T CELLS

Young AIREs go on to rule

Humans and mice with mutations in the autoimmune regulator (*AIRE*) gene develop a multi-organ autoimmune disease. The expression of AIRE during the first few weeks of life is necessary and sufficient to protect against the development of this disease. Reporting in *Science*, Yang *et al.* show that AIRE promotes the development of a distinct population of forkhead box P3 (FOXP3)-expressing $CD4^+$ regulatory T cells (T_{Reg} cells) during the perinatal period and that these cells protect a specific set of tissues from autoimmune attack.

AIRE induces the promiscuous expression of peripheral tissue antigens in medullary thymic epithelial cells (mTECs), the processing and presentation of which is necessary for T cell selection. mTECs can positively select T_{Reg} cells in the thymus, so the authors first assessed the impact of AIRE deficiency on T_{Reg} cell development over time. They found that the percentage and the number of T_{Reg} cells were reduced in $Aire^{-/-}$ mice compared with wild-type mice during the perinatal period. Furthermore, mice in which $FOXP3^+$ T_{Reg} cells were conditionally depleted during the day 0–10 developmental window showed multi-organ autoimmune disease typical of $Aire^{-/-}$ mice, even though normal T_{Reg} cell numbers were restored by day 11–12. The transfer of T_{Reg} cells from 20-day-old wild-type mice, but not from $Aire^{-/-}$ mice, prevented disease development in these perinatally T_{Reg} cell-depleted mice. These data indicate that AIRE promotes the perinatal generation of T_{Reg} cells that protect against multi-organ autoimmune disease. Of note, the autoimmune disease that develops in the absence of AIRE is restricted to a limited set of tissues and is distinct from that which occurs in mice that constitutively lack T_{Reg} cells or mice in which T_{Reg} cells are depleted during adulthood.

> “perinatal T_{Reg} cells are functionally distinct from adult T_{Reg} cells”

Annaïck Guitteny Photography

To assess the phenotype and function of perinatally generated T_{Reg} cells, the authors used mice in which all $FOXP3^+$ cells are marked with green fluorescent protein and a subset of cells that expressed FOXP3 at the time of tamoxifen administration are also marked with yellow fluorescent protein; in this study, tamoxifen was administered from days 0–10 (‘perinatally tagged’) or days 35–45 (‘adult-tagged’) after birth. Perinatally tagged T_{Reg} cells were shown to persist for at least 8 weeks after birth, although the percentage of these cells within the T_{Reg} cell compartment dwindled over this time as the total number of T_{Reg} cells exponentially increased.

An analysis of the labelled T_{Reg} cells showed that perinatally tagged T_{Reg} cells: had higher transcription of genes associated with T_{Reg} cell effector function; performed better in an *in vitro* suppression assay; were more activated; and proliferated better than adult-tagged T_{Reg} cells. Furthermore, the transfer of perinatally tagged T_{Reg} cells, but not adult-tagged T_{Reg} cells, into newborn $Aire^{-/-}$ mice prevented the development of the multi-organ autoimmune disease that typically occurs in these mice, which indicates that perinatal T_{Reg} cells are functionally distinct from adult T_{Reg} cells.

Further analysis identified age-dependent (but AIRE-independent) differences in the antigen processing and presentation machinery of mTECs, with ~50% of perinatal mTECs having low or no expression of CLIP (class II-associated invariant chain peptide), which occupies the peptide-binding groove of MHC class II molecules and must be dislodged to allow for peptide loading. Therefore, the repertoire of peptides presented by perinatal mTECs would be expected to be more diverse than adult mTECs. In addition, the T cell receptor repertoire of T_{Reg} cells from perinatal and adult mice was distinct.

AIRE promotes the perinatal development of a distinct population of T_{Reg} cells that protects a subset of tissues from autoimmune attack. However, further investigation is required to understand the link between AIRE and the age-dependent differences in antigen processing and presentation in mTECs and how this contributes to perinatal T_{Reg} cell development.

Olive Leavy

ORIGINAL RESEARCH PAPER Yang, S. *et al.* Regulatory T cells generated early in life play a distinct role in maintaining self-tolerance. *Science* http://dx.doi.org/10.1126/science.aaa7017 (2015)