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How cells switch from killers to helpers

Researchers illuminate a pivotal network of closely linked checkpoints controlling the destiny of key immune cells.

A cell's fate - how it progresses from an immature state into one that is specialized for a particular purpose - is a vital but poorly understood area of biology. In a critical and exciting breakthrough in this field, a team of scientists from the RIKEN Research Center for Allergy and Immunology, the Japan Science and Technology Agency's Precursory Research for Embryonic Science and Technology (PRESTO), and the Kyoto Prefectural University of Medicine, have described that newly uncovered details of how special immune cells commit to a specific lineage.

In the mammalian thymus gland, precursor white blood cells mature and finally develop into 'T' (for thymus-derived) cells. As integral components of the vertebrate body's elaborate adaptive immune system, T cells must constantly probe their environment, using a variety of 'CD' proteins and the T cell receptor (TCR) expressed on the cell surface, for the presence of invading pathogens.

TCR and CD proteins work closely together to identify major histocompatibility complex (MHC) proteins, which are specialized guidepost signals displayed on all cell surfaces. Cells communicate their status to the immune system by using MHC proteins to advertise antigens - processed protein molecules that stimulate an immune response - through which the cells exchange critical information, allowing the immune system to distinguish friend from foe.

All immature T cells express two special CD proteins, CD4 and CD8, but the two main subsets of functionally distinct mature T cells are defined by which one of these proteins is eventually NOT displayed. Hence, $CD4^{+}CD8^{-}$ helper T cells (TH) - which warn the immune system of pathogen invasions and also help to harmonize a coordinated immune response - only express CD4, whereas $CD4^{-}CD8^{+}$ killer T cells (TK) - which actually kill cells that have been infiltrated - express only CD8. Two versions of MHC proteins, class I - recognized by TK - and class II - recognized by TH - are important drivers for this critical cell fate determination but much remains unknown.

Th-POK - a DNA-binding protein that regulates gene expression - was recently identified as the main regulatory switch controlling T cell differentiation. Cells that engage class II MHC complexes activate *Th-POK* expression, which in turn induces CD4 production while simultaneously suppressing CD8 production, thereby committing the cells to the TH line. The team has now linked other key mechanistic components to this Th-POK switch.

The group had previously identified another family of DNA-binding proteins, called Runx, which repress CD4 expression in immature and mature T cells, as important determinants of T cell fate. Knowing that TK numbers are dramatically reduced when Runx proteins are absent or inactivated, the scientists sought to understand how this happens by examining genetically engineered mice that expressed mutant Runx protein but not MHC class II proteins. The majority of MHC class I-restricted cells in these special mice differentiated into $CD4^+CD8^-$ T cells that carry the TH $CD4^-$signature and were also functionally similar to TH.

Th-POK gene expression levels were elevated in these Runx mutant mice and because Runx protein complexes bound selectively to specific DNA sequences lying upstream of *Th-POK*, the Runx proteins must somehow mediate the repression of *Th-POK*. The team created mutant mice that were missing distinct portions of this putative *Th-POK* regulatory region and found that these mutant mice had much higher *Th-POK* expression levels than normal mice did. The scientists termed this control region the *Th-POK* silencer, concluding that it is a key determinant for regulating *Th-POK* expression levels, and that this silencer activity is in turn dependent on Runx binding complexes.

The researchers posit that other molecular players are needed to effect the Runx silencing activity and that there is a complex antagonistic interplay between *Th-POK* and Runx elements. Future studies will no doubt shed more light on the genetic programming that refines and defines our immune systems.

Original work:

Setoguchi, R., Tachibana, M., Naoe, Y., Muroi, S., Akiyama, K., Tezuka, C., Okuda, T., Taniuchi, I.
Repression of the Transcription Factor Th-POK by Runx Complexes in Cytotoxic T Cell Development. *Science*, published online on Feb. 8, 2008

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