Immunology

Guide for a cell-fate decision

Ellen A. Robey

How does an immature cell know how to develop into a specialized one? A fortunate observation has revealed one of the cues that guide precursor immune cells to their ultimate fate.

During the development of multicellular organisms, precursor cells mature into specialized cell types, such as muscle cells or blood cells. This cellular differentiation must be carefully orchestrated to generate the correct numbers and types of cells at the right time and place. Unravelling the regulatory circuitry involved is a major goal of developmental biologists. In a striking illustration of Louis Pasteur's famous statement, "Chance favours only the prepared mind", a fortuitous mutation in a mouse has led Kappes and colleagues to a breakthrough in understanding how immune-cell precursors adopt their appropriate cell fate (He *et al.*¹, page 826 of this issue).

In the mammalian thymus, precursor cells called thymocytes give rise to two types of mature immune cell: CD4 helper T cells, which alert the immune system when the body is invaded by a pathogen and coordinate an inflammatory response; and CD8 killer T cells, which destroy cells that have been invaded. Each T cell has receptors for a specific antigen on its surface. The gene that encodes these receptors is rearranged during the cell's development to produce one of a

huge potential variety of receptor genes. The range of receptors consequently produced by the entire population of mature T cells allows the immune system to recognize virtually any pathogen. These T cells probe other cells they come across, and respond when they find 'foreign' peptides that might signal the presence of a pathogen. The foreign peptides become bound to molecules of the major histocompatibility complex (MHC) and are displayed on the surface of invaded cells and other immune cells. The MHC comes in two varieties: class I, which is recognized by the CD8 killer T cells, and class II, which is recognized by the CD4 helper T cells. The CD8 and CD4 proteins aid the interaction between the MHC and the T-cell antigen receptor (Fig. 1).

In the thymus, immature T cells express both CD4 and CD8. The cells test whether their newly formed antigen receptors can bind to MHC complexes on thymic epithelial cells that display 'self' peptides, derived from the body's own proteins. Most of the thymocytes fail the test and die. Remarkably, binding to the peptide–MHC complex not only leads to the survival of thymocytes, but also directs them to the appropriate lineage:

Figure 1 The anatomy of a cell-fate decision. In the thymus, immune-cell precursors called thymocytes receive positive selection signals when their T-cell receptors (TCRs) recognize 'self' peptides (red circles) bound to molecules of the major histocompatibility complex (MHC) displayed on thymic epithelial cells. This interaction is helped by the CD4 or CD8 proteins. **a**, The thymocyte recognizes class II MHC, and receives a moderate, prolonged signal. This leads to production of Th-POK, a gene-regulatory protein that in turn controls other genes (including repression of the CD8 gene), causing the cell to adopt a CD4 fate. TCR signalling may also work independently of Th-POK (dashed line) to promote the differentiation or survival of CD4 cells. **b**, The thymocyte recognizes class I MHC, and receives a weak, transient TCR signal that fails to increase production of Th-POK. TCR-induced events in the absence of Th-POK lead to changes in gene expression (including repression of the CD4 gene), causing the cell to adopt the CD8 fate.

recognition of class I MHC leads to development of a CD8 T cell, and recognition of class II MHC leads to development of a CD4 T cell (Fig. 1).

The work by Kappes and colleagues¹ defines the molecular trail from the thymocyte–MHC interaction to the change in gene expression that guides the cell to its ultimate fate. While screening mice bred from two lines carrying different genetically engineered mutations, the authors noted² that some of the progeny had an unusual characteristic that was not the result of either mutation — a complete absence of mature CD4 T cells. A spontaneous mutation, which they termed 'helper deficient', or HD, was responsible for the defect. Further analysis revealed that HD did not simply cause loss of CD4 cells, but rather produced a 'cell-fate switch' by which thymocytes that would normally have matured into CD4 T cells instead gave rise to CD8 T cells³.

Although there are a number of engineered mutations that can also redirect the CD4 versus CD8 fate decision (reviewed in refs 4, 5), most of these mutations lead to proteins that have abnormal functions (rather than causing disruption of a normal function), and thus they may not reflect the true functions of the unmutated genes. Furthermore, most of these engineered mutations cause only a fraction of thymocytes to make the wrong cell-fate choice. HD is the only mutation known that not only is a loss-of-function mutation, but also causes a wholesale conversion of thymocytes from the CD4 to the CD8 lineage, and so it seems to hold the key to understanding this cell-fate decision.

Seven years after the original description of the HD mutation, Kappes and colleagues¹ have now identified the gene affected by it. It encodes a transcription factor called Th-POK (for T-helper-inducing POZ/ Krüppel factor). Transcription factors regulate gene activity, often in a tissue-specific manner. The discovery, therefore, that the HD mutation changes an amino acid of a transcription factor made perfect sense. The authors also show that, in the thymus, Th-POK is found specifically in mature CD4 T cells, and not in CD8 T cells. Moreover, enforced expression of the Th-POK gene in thymocytes transforms cells that would have been CD8 into CD4 cells, the opposite effect to the HD mutation. Thus, Th-POK is necessary and sufficient to induce the gene-expression programme for a CD4 cell fate and to suppress the CD8 programme.

Other transcription factors have been implicated in T-cell development, including GATA3, which is required for CD4 T-cell maturation^{6,7}, and Runx3, which silences the gene encoding CD4 in CD8 T cells⁸. However, mutation of their corresponding genes does not cause a cell-fate switch, but merely impairs the development of one cell

100 YEARS AGO

A Grass-snake which the writer had in his possession for eighteen months has just died. A fact which seems worthy of a note is the length of time during which this snake fasted. The last time the snake fed was June 11, 1904, the meal consisting of a small frog. From that time until the date of its death, February 2, it took no food, although constantly offered it. The animal thus existed for close on eight months without food. During the whole of this time it appeared in good health, and was, at times, most animated. No approach to hibernation was observed, and only for a little more than a week before its death did the snake seem out of health. The body was not unduly thin. From *Nature* 23 February 1905.

50 YEARS AGO

The organization for the fishing and conservation of the *Cœlacanth*s of the Comoro Islands created by the Institut de Recherche Scientifique de Madagascar... reports a new success: on November 12 last a further *Latimeria* was captured at Anjouan. This brings the total since 1938 to eight and is the finest yet, as regards both size and state of preservation, and by far the most interesting because it is the first near-adult female specimen which has come into our hands as well as the first of these precious fishes which anyone has been able to observe alive... Throughout the night — which the delighted population of Mutsamudu passed in singing and dancing to celebrate the capture — the *Cœlacanth* was watched over with admirable care by the chef de circonscription, taking turns with his adjoint, M. Solère. It seemed, although quite bewildered at the sequel to its ascent to the surface, to be taking the situation very well, swimming slowly by curious rotating movements of its pectoral fins, while the second dorsal and anal, likewise very mobile, served together with the tail as a rudder. After daybreak it became apparent that the light, and above all the sun itself, was upsetting the animal very much [and] the fish began to show more and more obvious signs of distress... At 14.45 hr. it was still swimming feebly; but at 15.30 hr. it had its belly in the air and only the fins and gill-covers were making agonized movements.

From *Nature* 26 February 1955.

type. So Th-POK seems to be at the top of a gene-regulation hierarchy that controls T-cell fate.

Many tantalizing questions remain. What controls expression of the Th-POK gene in developing thymocytes? The observation that Th-POK synthesis is increased in thymocyte precursors that recognize class II MHC, but not class I MHC, implies that the gene's expression is regulated by engagement of class II MHC. This may be controlled by differences in T-cell receptor signalling on recognition of class I compared with class II MHC, as predicted by a popular model for CD4 versus CD8 lineage commitment (reviewed in refs 4, 5). Further analysis of the regulation of Th-POK by T-cell-receptor signalling will be needed to test this idea.

What genes are regulated directly by Th-POK? The gene-expression programmes of CD4 and CD8 cells differ in terms of the production of GATA3, perforin (a T-cell effector protein), and CD4 and CD8 themselves. However, it is not yet clear whether these differences in gene expression are direct or indirect consequences of Th-POK activity.

Finally, self-reinforcing feedback loops are often used to 'lock in' cell-fate decisions, and there are hints that Th-POK is part of such a regulatory circuit. HD mice expressing class II MHC, but not class I MHC, show increased synthesis of messenger RNA for Th-POK in thymocyte precursor cells. However, the redirected CD8 T cells that ultimately develop in these mice lack Th-POK. Whether the requirement for Th-POK

function to maintain Th-POK gene expression involves auto-regulation of the gene or involves other components of the gene regulatory hierarchy remains to be seen.

The quest to understand the CD4 versus CD8 lineage decision has focused mostly on the question of whether MHC recognition instructs the cell-fate decision (the instructive model), or whether cells choose their fate randomly and are then tested for the presence of the appropriate CD4 or CD8 molecule (the stochastic or selection model)^{9,10}. These models, although useful, assumed that T-cell fate determination occurs as a single discrete step, but it has become clear that it is a multi-step process involving feedback and reinforcement. The identification of Th-POK as a key in the T-cell fate decision should open the way to deeper mechanistic insights into how cells are guided to their destiny. ■

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Planetary science

Being there

Kevin Zahnle

The protoplanets that collided to make the Earth may themselves have had atmospheres and oceans. Venus has vastly more argon and neon than Earth: fossil evidence, perhaps, of protoplanetary atmospheres?

Noble gases are the flotsam of the Solar System. They seem simple: they shun chemistry, they are difficult to freeze, and they accumulate in atmospheres. We see them as passive tracers of our cosmogonic theories, especially theories that address the origin and evolution of planetary volatiles. Perhaps it is a measure of our theories that every newly probed atmosphere has surprised us. Yet the temptation to read profound meaning into noble-gas abundances remains strong. On page 842 of this issue, Genda and Abe¹ ask whether atmospheres can survive a series of giant impacts, such as the collision with Earth that formed our Moon. The answers are ambiguous, with argon agreeable but neon cryptic.

Current fashion posits four stages in the growth of an Earth: coagulation of grains into boulders; gathering of the boulders into aggregates of kilometre dimensions; runaway accretion of those aggregates into Moon-sized protoplanets; and giant collisions between the protoplanets to make planets². The first three stages are thought to have taken no more than a million years in total, whereas the fourth played out over tens of millions of years or more.

Given how quickly stages 1–3 occurred, there is a fair likelihood that significant nebular gas was still present when the protoplanets emerged from runaway accretion. If the nebula was cold enough, and the protoplanets large enough, they would gravitationally capture significant primary atmospheres.