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Between B cells and T cells

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Mature cells develop through a number of immature stages. During this process, they must remember the specialization they are committed to. For immune system B cells, Rudolf Grosschedl of the Max Planck Institute of Immunobiology and Epigenetics and his team have discovered that the transcription factor EBF1 is crucial for B cells to remember who they are. When the researchers switched off the transcription factor, the cells lost their previous identity and developed into T cells. Unlike most other cell types, B cells have a characteristic footprint in their genetic makeup and this allowed the researchers to identify the origin of each individual cell.

During the transition from stem cells to becoming a functional part of the immune system, cells must undergo a number of specialization stages where they have the opportunity to decide between pathways leading to the various cell types found in the blood. It is also important that once they have chosen a specialization, they remain committed to it.

Immune system B and T cells come from the same stem cell. Rudolf Grosschedl and his colleagues were able to prove as early as 1995 that the transcription factor EBF1 is active only in some of these cells and this induces their development into B cells. Until now, however, it was unclear whether EBF1 also played a part in constantly reminding the B cells of their identity.

B cells usually die when EBF1 is switched off. In collaboration with researchers from the University of Freiburg, the Max Planck researchers collected mouse B cells at a late stage of their development and

transferred them to mice lacking an immune system. They then switched off the EBF1 gene in the transplanted B cells. After three months, they checked whether immune cells were still present in the mice. "We thought that the chance of this transfer enabling the cells to remain alive was slim, so we were very pleased that it worked," says Robert Nechanitzky, a doctoral student and first author of the study. The researchers did indeed find immune cells, but the B cells had forgotten their previous identity. In their place were T cells and natural killer cells, which normally would not be found in these animals.

To find out whether the T and natural killer cells actually had come from the transplanted B cells, the researchers looked for the specific genetic footprint of B cells. Unlike most other cells in the body, B cells change their DNA sequence during their development. To produce antibodies, they bring together several gene segments by cutting and joining their DNA to create a sequence able to code for a functional antibody. The researchers found precisely this typical genetic footprint of B cells in both T cells and natural killer cells. They concluded that after the transcription factor EBF1 had been switched off, the transplanted B cells had forgotten their specialization and had turned into alternate cell types. Until now, it was only known that the absence of the transcription factor Pax5 had such an effect. "We believe that the two proteins regulate different aspects of cell type specification. EBF1 primarily represses genes that would initiate an alternative program of development in the B cells, while Pax5 ensures that they no longer react to signals that would enable them to select a different specialization," says Grosschedl.

The Freiburg-based researchers now want to understand the exact molecular interactions in the cells and better define the network of factors involved. In the long term, they hope this knowledge will allow cells to be reprogrammed, for example in the case of a pathological loss of a cell type.

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