

Bcl6 gene sculpts helper T cell to boost antibody production

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Expression of a single gene programs an immune system helper T cell that fuels rapid growth and diversification of antibodies in a cellular structure implicated in autoimmune diseases and development of B cell lymphoma, scientists at The University of Texas M. D. Anderson Cancer Center reported today in *Science Express*, the advance online publication of the journal *Science*.

The gene is Bcl6, which the team found plays the crucial role in differentiating a naïve [T cell](#) into a T follicular helper cell (Tfh).

"Tfh cells were first noticed in structures called germinal centers found in the lymphoid system - in lymph nodes and the spleen," said senior author Chen Dong, Ph.D., professor in M. D. Anderson's Department of Immunology. Germinal centers are powerful machines that churn out lots of antibodies.

In the adaptive immune system, B cells present an antigen - a distinctive piece of an invading bacterium or virus - to T cells. The bound antigen converts a naïve T cell to a helper T cell that secretes cytokines which help the B cells expand and produce a large volume of antibodies to destroy an intruder.

Tfh cells are concentrated with B cells in germinal centers, where they play a helper T cell's traditional role in B cell proliferation and antibody development.

"In germinal centers, the B cells not only proliferate but they also undergo hypermutation in their immunoglobulin genes so they can produce a diverse class of antibodies," Dong said. "These mutations also allow production of [antibodies](#) with stronger affinity for their target antigens."

There are pitfalls to this process. Tfh cells and germinal centers have been implicated in antibody-mediated [autoimmune diseases](#) such as lupus and rheumatoid arthritis, Dong noted. In these diseases, the germinal centers are likely producing the wrong type of antibody at great volume.

Genetic hypermutation among B cells in germinal centers creates a hotbed of genomic instability, which gives rise to some types of B cell lymphoma, Dong said.

The scientists set out to understand the role of Bcl6, which is short for [B-cell lymphoma 6](#), a transcription factor previously shown to be selectively expressed in Tfh cells.

Last year, Dong and his colleagues reported in the journal *Immunity* that cytokines IL-6 and IL-21 drive the differentiation of Tfh cells. However, how these cytokines work had been unclear. In the current study, the team reported that that IL-6 and IL-21 induce expression of Bcl6 in the absence of transforming growth factor beta (TGF β) to drive T cell differentiation into Tfh. "Not only is Bcl6 a transcription factor expressed by Tfh cells, it also has a major function in generating these cells," Dong said.

When TGF β is present with IL-6 and IL-21, T cells differentiate into pro-inflammatory Th17 helper cells.

Another set of experiments showed that Bcl6 expression inhibits a T cell

from differentiating into Th17, Th1 or Th2 cells, three other lines of helper cell

Finally, when the Bcl6 gene was knocked out in a mouse model, Tfh was nowhere to be found. "Bcl6 is absolutely required for Tfh generation and it's also important because it blocks other pathways that would lead the T cell into other helper cell types," Dong said.

Solving the molecular programming of Tfh establishes it as the fifth distinct lineage of helper T cell.

Dong and colleagues will continue to characterize Tfh and its relationship to other T helper cells. Dong is co-discoverer of the Th17 cell, which he and colleagues identified as the third T helper cell lineage when conventional wisdom held that there were only two such lines. They also showed that Th17 secretes interleukin-17, which is implicated in both inflammatory and autoimmune diseases.

Source: University of Texas M. D. Anderson Cancer Center ([news](#) : [web](#))

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