Gene knockout stops immune cell development

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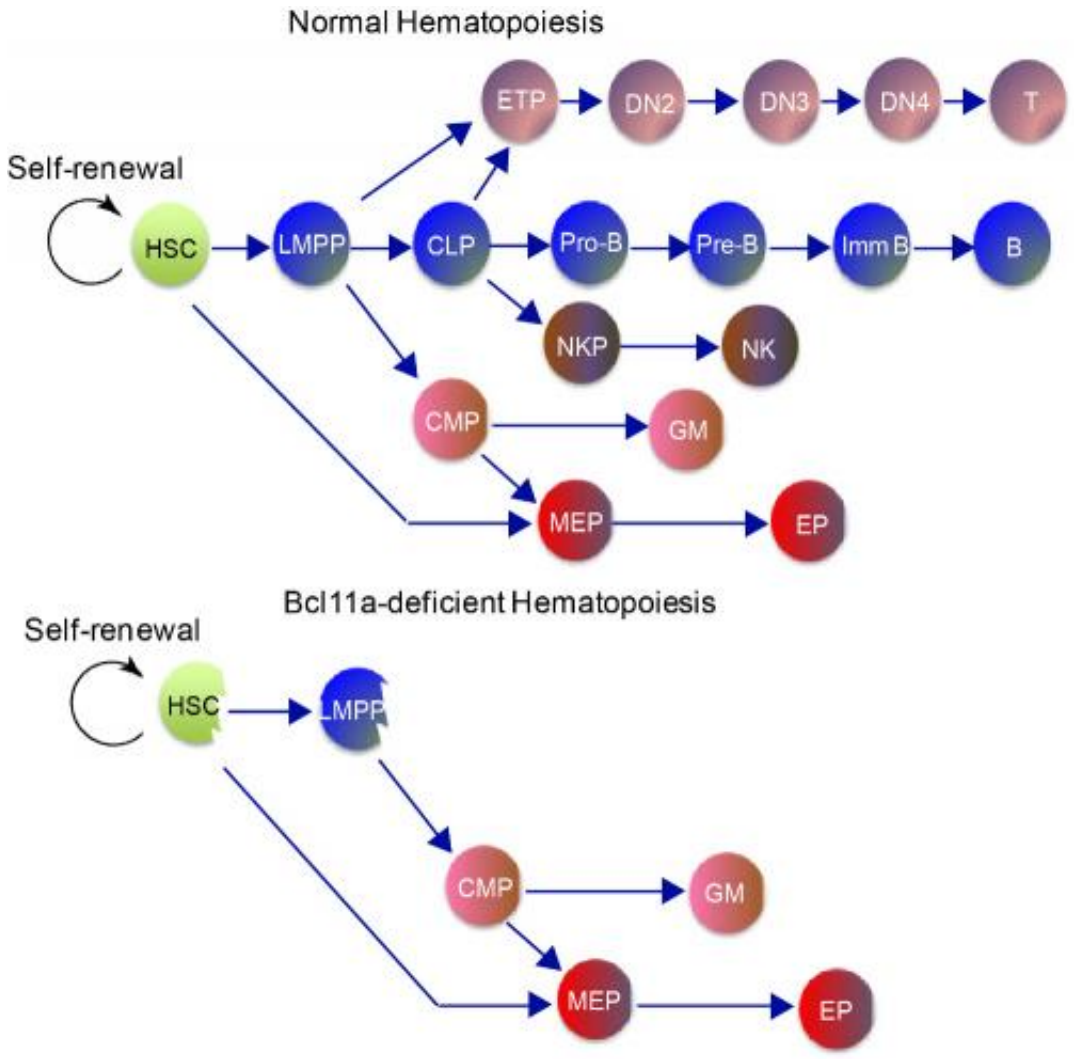

The working model of Bcl11a in hematopoiesis. Credit: Yong Yu, Genome Research Limited

(Medical Xpress)—Researchers at the Wellcome Trust Sanger Institute have identified the key gene in ensuring that our immune defences develop infection-fighting cells. No cells of the adaptive immune system - key to attacking and destroying bacteria and other pathogens - develop in the absence of the gene Bcl11a.

The result will help to understand the human immune system and how it can fail in disease, as well as possibly allowing the development of functioning human immune systems in mice for research and development of treatments.

Our immune system has two arms: the adaptive and innate pathways. The adaptive immune system leads to infection- and cancer-fighting cells called B cells, T cells and NK cells: these all share a common ancestor, or lymphoid progenitor.

The team had shown earlier that Bcl11a was important for development of some immune cells in mouse embryos. In the new research they looked at the role of this gene in adult mice. They knocked out Bcl11a and looked at development of the immune system cells.

They were surprised to see that no cells of the adaptive system developed in the mice.

"This is the cornerstone of building an effective immune system," says Dr Pentao Liu, who led the research. "It is perhaps the first time that anyone has found a single gene that is absolutely essential for development of cells of our entire adaptive immune system.

"With this new discovery, we can understand better how our immune system is built and begin to learn how we might repair it."

The protein produced by Bcl11a controls the activity of other genes: it is

part of a network of components that regulate cell development and the imbalance caused by a lack of Bcl11a leads to the death of the progenitor cells of the adaptive immune system. By contrast, overactivity of Bcl11a is known to cause lymphomas.

"This is the most important gene in the adaptive immune system," says PhD student Yong Yu, who did the research while at the Wellcome Trust Sanger Institute. "Without it, there are no cells of this system, no antibodies to fight infection.

"We have begun to tease apart the networks that have to work in balance to give us a healthy immune system."

One member of the Bcl11a network is a gene called p53, known to be important in controlling cell division and, when mutated, important in driving cancer development. If p53 also is inactivated in mice that lack Bcl11a, some cells of the immune system develop. Uncovering these interactions will drive a better understanding of disease of the immune system.

Mice that lack functional Bcl11a and hence lack a functional immune system could be important in studying human cells and human immune biology. By adding human disease cells to the immune-deficient mice, researchers could define the function of human genes in a humanised environment in order, for example, to examine the role of genes in transplant biology.

Bcl11a also has a role in development of oxygen-carrying red blood cells: in 2011, researchers showed that silencing Bcl11a in mice could reverse sickle-cell disease.

"Our discovery shows that Bcl11a has a central and essential role in the immune system, alongside its other functions," continues Dr Liu. "It is

work that our mouse models have driven. Understanding the complex interactions of networks of genes in this way will be essential for better understanding human disease and in finding better ways to diagnose and treat patients.

"We already see that Bcl11a is involved in lymphoma and anaemia. We can now look to see if it has a role in other human disease."

More information: Yu, Y et al., Bcl11a is essential for lymphoid development and negatively regulates p53, *Journal of Experimental Medicine* 2012
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