# Researchers discover fundamental step in immune-system development

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Researchers at National Jewish Health have discovered a fundamental step in the development of the immune system, one that allows B cells to mature and fight disease by producing effective antibodies. Immunologist Roberta Pelanda, PhD, and her colleagues have demonstrated that immature B cells in the bone marrow must receive a positive signal before they can migrate to the spleen where they mature and are activated. In the March 15, 2010 issue of The *Journal of Experimental Medicine*, the researchers also reported that a protein known as Erk helps deliver that positive signal.

"Our work demonstrates that the immune system uses both positive and negative selection processes to create an effective population of B cells," said Dr. Pelanda, Associate Professor in the Integrated Department of Immunology at National Jewish Health and the University of Colorado Denver. "A defect in either selection process could lead to autoimmunity or immune deficiency."

Humans make millions of B cells every day, each one equipped with its own unique B-cell receptor. Each receptor recognizes a specific protein fragment. Once the receptor recognizes that fragment, the B cell becomes activated and releases antibodies that attack the protein or the cell it is on.

B-cell receptors first appear on developing B cells in the bone marrow. Some of those receptors bind to proteins that are a normal part of the body, and could trigger an autoimmune attack. Other receptors can be

non-functional. The selection process weeds out these dangerous and non-functional B cells to produce a population that can recognize a wide variety of foreign, potentially harmful invaders, but tolerate proteins that are a normal part of the organism.

Negative selection occurs in the bone marrow when potentially autoimmune B cells are detected, rejected and instructed to produce a different receptor.

The next step has been unclear. Do B cells that survive negative selection leave the bone marrow on their own? Or do they need a signal that tells them to leave the marrow and migrate to the spleen?

Dr. Pelanda and her colleagues knew that B-cell receptors deliver a constant, or 'tonic,' signal, even when they are not activated. They thought that tonic signal might direct appropriate B cells to leave the bone marrow, migrate to the spleen and mature.

Using a unique mouse model and an in vitro system designed specifically for B cells, Dr. Pelanda found that mice who make fewer B-cell receptors have fewer mature B cells in their spleens. The B cells could have left the bone marrow but died because they did not have a B-cell receptor, known to be necessary for survival. If that were the case, then a pro-survival factor, bcl-2, should have rescued mature B cells and increased their population. It did not. Thus, it became clear that immature B cells must receive a signal from the B-cell receptor that allows them to escape the bone marrow, migrate and mature.

"It is a very important checkpoint," said Dr. Pelanda. "Without it, B cells are stuck in the bone marrow, unable to circulate, mature and contribute to immune defense."

Dr. Pelanda and her colleagues then activated the protein Erk by turning

on the Ras gene, and saw that more B cells escaped the bone marrow to mature. Conversely, when they blocked activation of Erk in normal B cells, few were able to mature. Thus, Erk helps deliver the positive-selection signal that allows B cells to mature.

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