

# Researchers find source of new lineage of immune cells

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The elusive progenitor cells that give rise to innate lymphoid cells—a recently discovered group of infection-fighting white blood cells—have been identified in fetal liver and adult bone marrow of mice, researchers from the University of Chicago report early online in the journal *Nature*.

Innate lymphoid cells (ILCs) are among the first components of the immune system to confront certain pathogens. They have a critical function at mucosal barriers—locations such as the bowel or the lung—where the body comes in direct contact with the environment. Yet they went undetected by researchers studying the immune system for a century.

"Scientists tend to look for immune cells in the blood, lymph nodes, or spleen," said study author Albert Bendelac, PhD, professor of pathology at the University of Chicago. "That is precisely where you would not find these cells. Once they mature they directly go to tissues, such as the gut or the skin. You seldom see them in blood."

To understand where these cells came from and how they fit into the ecosystem of cells that fight off infection and cancer, Bendelac's team focused on finding the source of ILCs.

Innate lymphoid cells, first recognized only five years ago, are rare. A mouse might have 200 million lymphocytes but only a few thousand ILCs. But researchers knew from previous work on NKT cells that innate lymphoid cells express an unusual transcription factor called PLZF

during their development. So they created so-called 'reporter' mice with the gene for green fluorescent protein inserted into mouse DNA, just downstream from the PLZF gene. As a result, cells from those mice that expressed PLZF appear bright green under the microscope.

Even though green-glowing cells stand out, finding the precursors to these lymphocytes, about one in 10,000 cells, was not easy. The precursors are not in the blood, and by the time they migrate to the lungs or gut, they have already matured into ILCs. The researchers eventually found the precursors to innate lymphoid cells (ILCPs) in the liver of fetal mice and in [bone marrow](#) of adult mice.

When the team purified the ILC precursors, which still contained the GFP gene, and transferred them into mice that lacked ILCs, the precursors were able to reconstitute the three known types of innate lymphoid cells. "There were no B cells or T cells or [myeloid cells](#), no other [immune cells](#), just these," Bendelac said. "So we think the ILCP really is a committed precursor to innate lymphoid cells."

To confirm their finding, the researchers designed mice where PLZF gene expression was tied to the gene for diphtheria toxin. When cells expressed PLZF, they also produced the toxin, which was lethal for those cells. The result was a mouse that had a normal [immune system](#) except that it completely lacked innate lymphoid cells.

Recent studies have demonstrated the importance of ILCs. They play key roles in protecting against infection or parasites, but they also have been implicated in autoimmune disorders.

Each of the three types of innate [lymphoid cells](#)—known as ILCs 1, 2 and 3—has different properties and serves different functions. ILC1 cells help prevent viral infections and can detect and remove some [cancerous cells](#). They are similar to natural killer (NK) cells, except that

NK cells circulate in the blood and ILC1s live in the gut and the liver. ILC2s are found in the lungs where they can detect and respond to parasites, but they also can initiate an allergic reaction and mucus hypersecretion. ILC3 cells cluster in the gut, where they help mediate interactions between the bowel and bacteria. When that balance is disturbed, they can accelerate inflammation and may play a role in inflammatory bowel disease.

"ILCs are found in the most exposed tissues," Bendelac said. "They are one of your first lines of defense. We now suspect they may also influence the ensuing adaptive immune response, priming the pump, influencing how T-helper [cells](#) respond."

"Our findings provide one more tool for understanding this complex system," Bendelac said. This will help generate "powerful new way to assess the function of innate lymphocytes."

**More information:** The paper, "A committed precursor to innate lymphoid cells," is available on the *Nature* website, at [DOI: 10.1038/nature13047](https://doi.org/10.1038/nature13047)

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