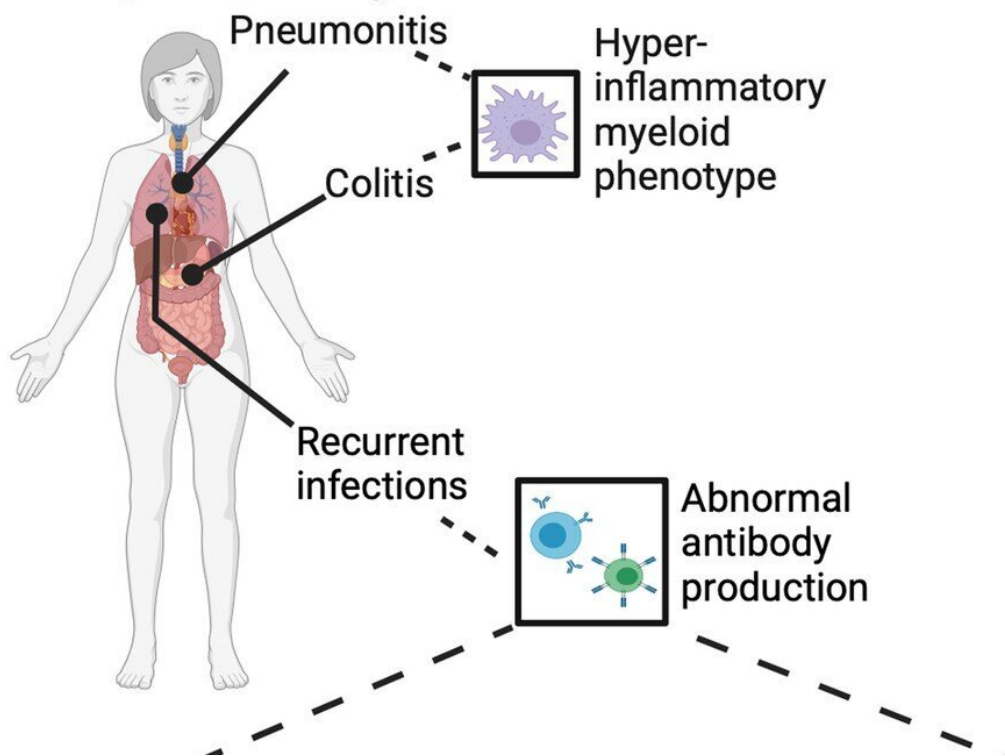


Patient-driven discovery reveals potential target for autoimmune diseases

July 16 2024, by Isabella Backman

PI3K γ Deficiency



Model summarizing the function of PI3K γ in antibody responses. Credit: *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01890-1

A medical mystery served as the genesis for a Yale-led study that has promising implications for treating a range of autoimmune diseases.

A young girl entered the clinic suffering from blood cell abnormalities, difficulty breathing, and later, diarrhea. She also had been diagnosed with recurrent infections due to low levels of antibody production. Her doctors treated her with corticosteroids to reduce her lung and gut inflammation and immunoglobulin replacement therapy to restore her antibody levels.

The lab of Carrie Lucas, Ph.D., associate professor of immunobiology at Yale School of Medicine, works with children living with rare immune disorders that stem from a single (monogenic) [gene mutation](#) with the goal of better understanding the intricate circuitry of human immunology.

Through [genome sequencing](#), Lucas discovered that the girl's symptoms were caused by mutations that created a deficiency in phosphatidylinositol 3-kinase-gamma (PI3K γ), a signaling molecule that is found in immune cells. Immune defects caused by this mutation, the research team found, were driving immune-mediated damage in the girl's gut and lungs, and also decreasing her antibody levels.

The team published its [initial discovery](#) in September 2019 in *Nature Communications*.

The discovery spurred Lucas' team to dig deeper into the biological connection between PI3K γ and antibody response. Now, the scientists have found that PI3K γ plays an essential role in allowing activated B cells, a type of immune cell, to differentiate into antibody-secreting cells.

Beyond helping understand disease from rare cases of human PI3K γ deficiency, the researchers hope that other patients can also benefit from this new knowledge.

By therapeutically blocking PI3K γ , clinicians might be able to treat the overproduction of antibodies that causes the symptoms of many autoimmune diseases. The team published its new findings in [*Nature Immunology*](#) on July 3.

"These sorts of monogenic, single-gene defect diseases help us learn fundamental biology directly from patients," says Lucas, who was the study's principal investigator. "We're excited that this could potentially help us find a new way to intervene in autoimmunity."

How do B cells become antibody-producing cells?

Antibodies are one of the key components of the adaptive (or acquired) immune system and target foreign invaders such as bacteria or viruses. B cells play a vital role in antibody production and in immune memory that protects us from reinfection.

B cells become activated when an antigen [a substance that triggers the body's immune response] binds to its receptors. Once activated, B cells form what are called "germinal centers."

"We think of germinal centers as factories for B cells to become optimal antibody secreters and choose cell fates to support that function," says Lucas.

B cells have multiple potential fates, including becoming memory cells or antibody-secreting cells (ASC). The role of memory cells is to "remember" specific antigens so that the body can more rapidly initiate an immune response if the antigen returns.

In turn, ASCs begin releasing very large amounts of antibodies that target the intruder into the blood. However, immunobiologists have not understood all the details of the differentiation process of B cells.

PI3K γ plays essential role in B cell differentiation

Inspired by their patient's genetic mutation and low [antibody levels](#), Lucas' team sought to explore the potential role of PI3K γ in antibody production.

First, they needed to create a mouse version of their human patient. So, the team used genetically modified mice in which PI3K γ was knocked out. Back in 2019, they tested these mice by emulating how humans, unlike 'clean' [laboratory mice](#), live in an environment filled with microbes.

"Knockout" and control lab mice were exposed to ones from a pet store, to introduce microbes into the lab mice that the animals had never experienced while isolated in the lab. The researchers found that the knockout mice (lacking PI3K γ) also had defective antibody production following exposure to these new antigens from the pet store mice. "This told us that this kinase is critical for antibodies in mice just as it is in humans," says Lucas.

Fast forward to their latest publication—now, the researchers wanted to know which specific types of immune cells use PI3K γ . So, they created various mouse models in which PI3K γ was knocked out of only one type of immune cell, such as B cells, T cells, macrophages, or dendritic cells. Then, they immunized the mice and measured antibody production.

They discovered that removing PI3K γ specifically from B cells created nearly identical reductions in antibody response to what they had seen in their patient. "This was our first dive into what was going on in the immune system—B cells require this kinase for them to function properly," says Lucas.

Next, the researchers wanted to elucidate what role PI3K γ plays in B

cells during an immune response. Their models revealed that PI3K γ was not important during activation or germinal center formation, but rather during a B cell's differentiation into an ASC.

PI3K inhibitors could potentially treat autoimmune diseases

Lucas is excited by these findings, which started with patient-driven discovery, and their relevance for human health. Her team identified not only a major player in how B cells choose to differentiate but also a potential target for treating autoimmune diseases. Current treatments for autoimmune diseases often include completely wiping out B cells. "This can be quite helpful but is also setting the patient up to be at risk for infections," she says.

PI3K inhibitors are already used to treat certain cancers and rare diseases. Could these drugs also help restore an overactive immune system? She wondered.

To begin to investigate, her group teamed up with Neil D. Romberg, MD, associate professor of pediatrics (allergy/immunology) at the Children's Hospital of Philadelphia, and his colleagues for studies in human tonsil organoid models.

After treating the models with a PI3K γ -targeting drug, the researchers found it successfully blocked B cells' ability to differentiate into ASCs. "This gives us direct human data paired with our mouse data to boost our confidence that our findings are relevant for shutting off ongoing antibody responses," Lucas says.

In future studies, Lucas' team plans to test PI3K inhibitors in pre-clinical autoimmunity mouse models to further evaluate them as potential

treatment options. Her team's work emphasizes how studying rare genetic diseases can also provide broader insights that are significant to a larger proportion of the population, she says.

"Here, we started with a patient, learned what gene is affected, and then followed that thread to find a new level of mechanistic understanding," she says. "This enabled us to take new insights that come from a totally different field—in this case, immunodeficiency—and now move toward applying it to autoimmunity."

More information: Stephen M. Lanahan et al, PI3K γ in B cells promotes antibody responses and generation of antibody-secreting cells, *Nature Immunology* (2024). [DOI: 10.1038/s41590-024-01890-1](https://doi.org/10.1038/s41590-024-01890-1)

Provided by Yale University

Citation: Patient-driven discovery reveals potential target for autoimmune diseases (2024, July 16) retrieved 16 July 2024 from <https://medicalxpress.com/news/2024-07-patient-driven-discovery-reveals-potential.html>

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