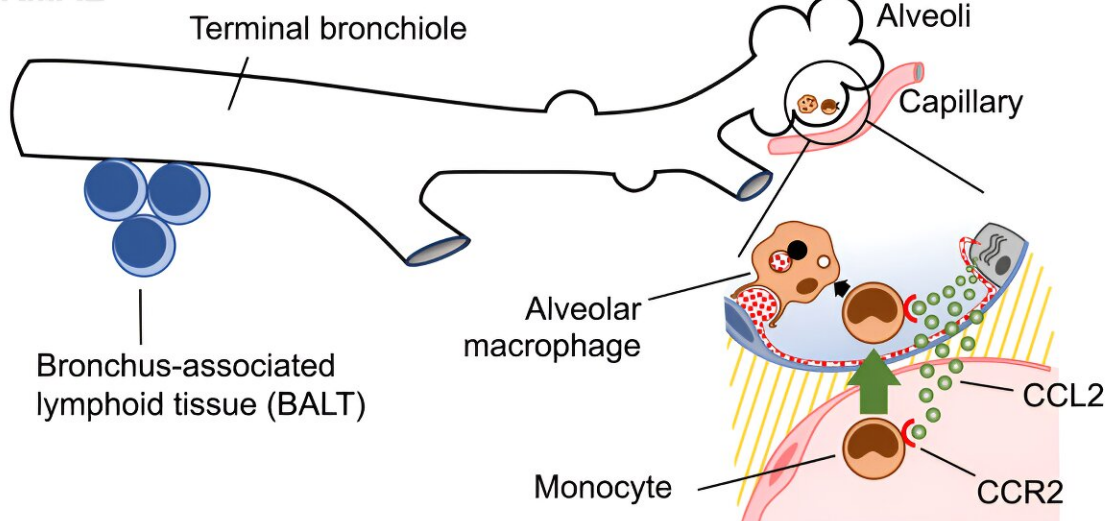


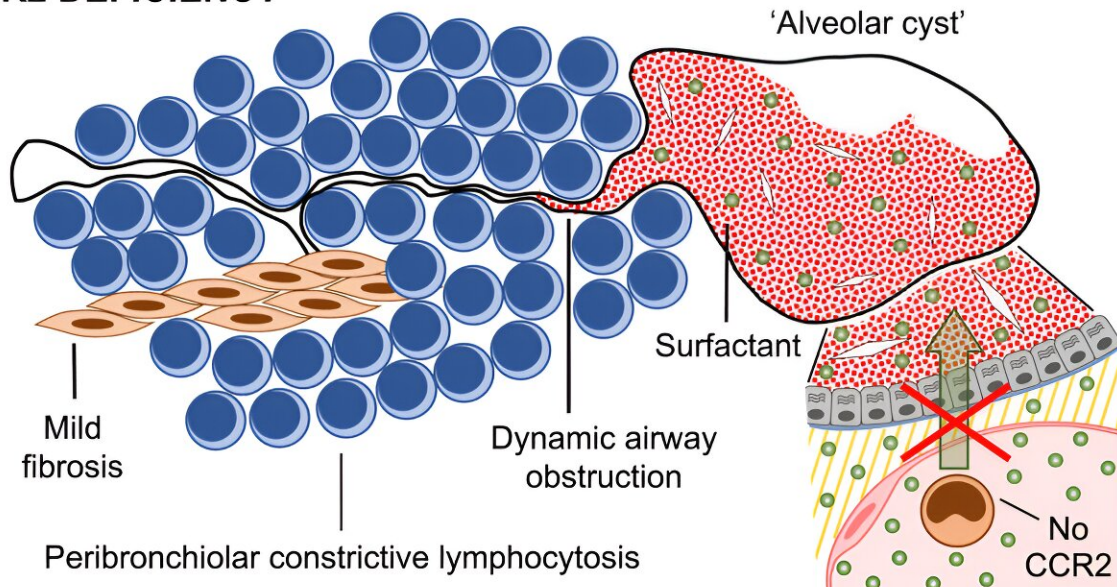
Newly discovered genetic malfunction causes rare lung disease

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NORMAL



CCR2 DEFICIENCY



Credit: *Cell* (2023). DOI: 10.1016/j.cell.2023.11.036

In a recent study, investigators from Rockefeller University and other institutions have discovered a never-before-documented genetic disorder that causes the improper functioning of macrophages.

The macrophage is one of the body's most important inhabitants. Meaning "big eater" in Greek, this immune cell consumes and digests problematic elements from microbes and cancer cells to dust and debris. Macrophages are especially important in the lungs, where they both fight bacterial infection and clear the lungs of excess surfactant, a protein- and lipid-rich layer that's essential to healthy function but can create a sticky buildup if not controlled.

In their study, the researchers made their discovery by drawing an unexpected connection among a select group of sick children. Throughout their lives, these nine children had battled severe diseases such as pulmonary alveolar proteinosis (PAP), progressive polycystic lung disease, and recurrent bacterial and [viral infections](#) that left them gasping for breath from often cyst-plagued lungs.

But as [genomic data](#) revealed, the children shared another characteristic: the absence of a chemical receptor that is supposed to call alveolar macrophages into action. It's the first time that this missing receptor, called CCR2, has been linked to disease. The researchers, including Rockefeller's Jean-Laurent Casanova and Institut Imagine's Anna-Lena Neehus, recently [published](#) their results in *Cell*.

The study also found that the children are missing half of their alveolar macrophages, which are located in the air sacs of the lungs.

"It was surprising to find that CCR2 is so essential for alveolar macrophages to properly function," says Casanova. "When it comes to lung defense and cleanup, people without it are operating at a double loss."

Chemical communication

More formally known as C-C motif chemokine receptor 2, CCR2 sits on the surface of alveolar macrophages, a kind of monocyte (or white blood cell). It responds to the presence of a chemical ligand, or binding molecule, known as CCL-2, which is also expressed by monocytes.

The receptor and ligand work together to summon macrophages to the site of an infection, and to maintain the appropriate level of surfactant; too little can lead to collapsed lung tissue, and too much can result in narrowed airways.

It was among these [immune cells](#) that first author Neehus, of Casanova's lab at the Institut Imagine in Paris, was seeking evidence of genetic deficiencies that might alter their behavior. While combing through the genomic data on 15,000 patients in a database, she found two Algerian sisters, then aged 13 and 10, who'd been diagnosed with severe PAP, a syndrome in which surfactant builds up and the gas exchange that takes place in alveoli is hindered.

About 90% of PAP cases are caused by antibodies that cripple a protein that stimulates the growth of infection-fighting white blood cells. The girls, however, didn't have the PAP autoantibodies. Instead, they had no CCR2—a newly identified genetic mutation. Perhaps its lack was connected to their pulmonary conditions, Neehus thought.

"It looked interesting and promising," she recalls.

She soon found seven other children in the cohort who had the same CCR2 mutation and serious lung conditions: two more pairs of siblings, and one trio of siblings. They were from the United States and Iran.

Diminished capacity

To explore the impact the variant might have on the children, the researchers analyzed the children's clinical histories, [lung tissue](#) samples, and genetic data.

Several key findings emerged. "First we discovered that these patients have only half the normal counts of pulmonary [alveolar macrophages](#), which explains the different types of lesions they have across the pulmonary tissues," says Casanova. With only half a crew, the reduced cleanup unit couldn't keep up with its workload, leading to tissue injury.

The macrophages were otherwise normal, as were the children's other immune cells.

Without CCR2 signaling, monocytes have no idea where they're needed. In the study, a live-imaging analysis of the monocytes from the lungs of a 10-year-old girl with CCR2 deficiency showed the cells milling about aimlessly, unsure where to go. In contrast, live imaging of monocytes from a healthy control patient shows them migrating in the same direction, summoned by the teamwork of CCR2 and CCL-2.

A troubled inheritance

This directionlessness also makes those with a CCR2 deficiency more susceptible to mycobacterial infections, because the macrophages can't find their way to the tissue clusters where mycobacteria take up residence, and thus digest the invaders.

This had dire effects for three of the children in the study, who developed bacterial infections after being vaccinated with a live-attenuated substrain of *Mycobacterium bovis*, an agent of tuberculosis. Their immune systems failed to assemble a legion of macrophages at the vaccination site in the shoulder, causing tissue destruction or hard nodes that had to be surgically removed, or lymph node infections. (All of the children were effectively treated with antibiotics.)

The children inherited the deficiency from their parents—and yet their parents were healthy. "Each of the parents carries one disease copy of the gene, and both parents gave the affected copy to their children," says Neehus. "The parents aren't affected because they each only have one copy, whereas the kids have two."

Several [children](#) were the result of consanguineous marriages, in which the parents are related. The offspring of such pairings have a higher risk of inheriting the mutation that causes CCR2 to disappear.

The diagnostic test

The absence of CCR2 leads to another effect: an excess of the chemokine CCL-2. Lacking its receptor, CCL-2 builds up in the blood and plasma. This outcome may provide a [diagnostic test](#) for screening patients with unexplained lung or mycobacterial disease; the detection of high CCL-2 levels could provide some clarity about the condition's genetic underpinnings.

In future research, Casanova and his team will mine their database of genomes for patients with gene mutations in CCL-2 rather than in its receptor, CCR2, to understand how such errors may influence the development of disease.

Neehus says, "With more follow-up studies, we could potentially cure

the patients by using gene therapy to correct the mutation."

More information: Anna-Lena Neehus et al, Human inherited CCR2 deficiency underlies progressive polycystic lung disease, *Cell* (2023).

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Provided by Rockefeller University

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