

The Importance of the Choline in Chronic Lung Infections

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The Importance of the Choline in Chronic Lung Infections

People with chronic lung conditions like COPD and cystic fibrosis are vulnerable to lung infections caused by the bacterium *Pseudomonas aeruginosa*. These infections are often difficult to treat and can cause sudden worsening of symptoms, known as flare-ups or acute exacerbations. While we know *P. aeruginosa* triggers inflammation and damage in the lungs, much less is understood about how exactly it causes these flare-ups, or how it survives in such a harsh environment. Dr Sandra Grumelli from the Center of Investigations of Respiratory Diseases in Argentina, has explored the role of a common molecule called choline which is released during infection. Using a combination of mouse models and laboratory experiments, she has discovered that choline not only makes breathing harder, it also helps *P. aeruginosa* adapt to and persist in the lungs. Her research opens up new possibilities for tackling chronic infections by targeting the bacteria's energy use and the way it responds to its environment.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (commonly known as COPD) is the name for a group of lung conditions that cause breathing difficulties. These conditions include emphysema, where the air sacs in the lungs called alveoli disappear. The walls in these sacs are usually stretchy, allowing them to fill with air. In people with COPD, it is harder for these sacs to inflate and deflate, causing difficulties with breathing. Another aspect of COPD is chronic bronchitis, when the lining of the airway becomes irritated and inflamed, leading to cough and overproduction of mucus.

In the United States COPD affects more than 14 million people and is the sixth leading cause of death, according to the Centers for Disease Control and Prevention. The most common COPD symptoms are shortness of breath, a persistent cough, and feeling very tired. COPD symptoms can suddenly get worse for a few days, known as flare ups or acute exacerbation which often need additional treatment. COPD happens when the lungs become damaged and inflamed often due to smoking, air pollution, or a genetic mutation. There is currently no cure or way to reverse COPD damage to the lungs because the air sacs disappear, but steroids and oxygen can help people through flare-ups.

During flare ups people may cough more, produce more mucus, struggle to breathe, and have to breathe faster to get enough oxygen. Normally the physical process of breathing uses only a little bit of the body's oxygen (about 5%), but during a flare up it can take a lot more effort (up to 250%) and oxygen just to keep breathing. This is partly because during a flare up there is more tissue resistance and the lungs can't breathe out carbon dioxide properly, causing it to build up the blood in a process called hypercapnia which makes the blood more acidic.

Cystic Fibrosis

Another condition which can lead to breathing difficulties, persistent coughs, and frequent lung infections is cystic fibrosis. This is a genetic condition, where a faulty gene is passed down by both parents, resulting in the production of thick mucus which affects the lungs and other body systems. Cystic fibrosis also currently has no cure, but similarly to COPD, treatments including steroids and inhaled medicines which widen the airways can improve respiratory symptoms.

Pseudomonas aeruginosa and Lung Diseases

Both COPD and cystic fibrosis make people more vulnerable to bacterial infections of the lungs and respiratory tract. A key bacterial species which can cause these infections is *Pseudomonas aeruginosa* (*P. aeruginosa*), this bacterium can cause infections in all parts of the body including the skin and gut but is notorious for causing hard to treat infections in people with underlying respiratory conditions.

Up to 20% of people diagnosed with COPD are infected with *P. aeruginosa*, and *P. aeruginosa* is the leading cause of lung infections in people with cystic fibrosis. Infection by *P. aeruginosa* in people with lung conditions can lead to a decline in lung function, increased symptom flare ups, and is associated with worse clinical outcomes and reduced lifespan. *P. aeruginosa* is able to release harmful substance within the lungs and respiratory tract during infections. The outer surface of the *P. aeruginosa* bacteria includes molecules called lipopolysaccharide or LPS, these trigger our immune system leading our body to release inflammatory molecules and enzymes which can further damage lung tissues and contribute to worsening of respiratory symptoms.



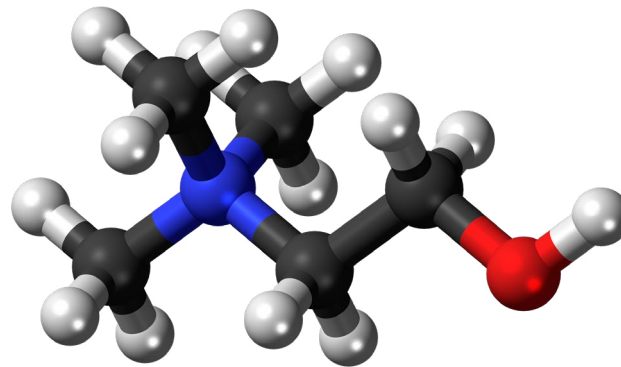
Despite being so hard to treat and a major cause of illness, little is known about how *P. aeruginosa* causes severe lung disease acute exacerbation. Dr Sandra Grumelli has led a team of expert researchers at the CIMeR in Argentina alongside scientists at Harvard Medical School to understand the molecular mechanisms between *P. aeruginosa* and lung disease symptoms.

The Importance of Choline

Choline is a naturally occurring molecule found in the membranes around cells and in surfactant, the slippery substance which helps keep our lungs open. As well as its LPS triggering the immune system, *P. aeruginosa* can also produce enzymes which break down the lung surfactant, as this breaks down it releases a molecule called choline. Choline can trigger the airways to narrow and change how blood vessels within the lungs behave, making breathing even harder.

Dr Grumelli and her team at Harvard Medical School conducted a series of experiments to find out if the production of choline by *P. aeruginosa* may actually be triggering the flare ups. The team used a mouse model to understand the role of *P. aeruginosa* in the development of respiratory flare up symptoms. First, they exposed some of the mice to cigarette smoke over time to create emphysema-like lung damage, they then added LPS from *P. aeruginosa* to mimic the lung inflammation that would be seen during infection to some of the mice. Choline was then given and the team conducted experiments to see how these factors affected the mouse lungs. They used a specialised machine to measure how hard the lungs had to work to breathe, including checking lung stiffness, resistance in the airways, and how much oxygen and carbon dioxide the mice were breathing in and out.

They also collected lung fluid samples to count the immune cells, and looked at lung tissue under a microscope to check for damage. They measured how much energy the mice were using and how the levels of carbon dioxide and acidity in their blood changed.



△ Choline.

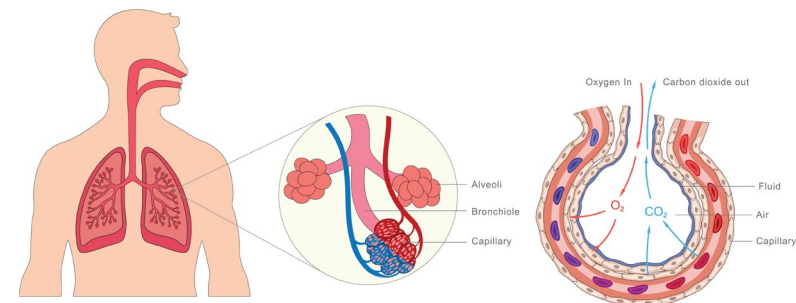
The team also wanted to understand how choline impacts *P. aeruginosa*, so in laboratory experiments they grew the bacteria using choline and a different molecule called succinate as its food source. They then assessed the levels of key molecules within the bacterial cells and speculated how this might impact the bacteria's behaviour within the human lung.

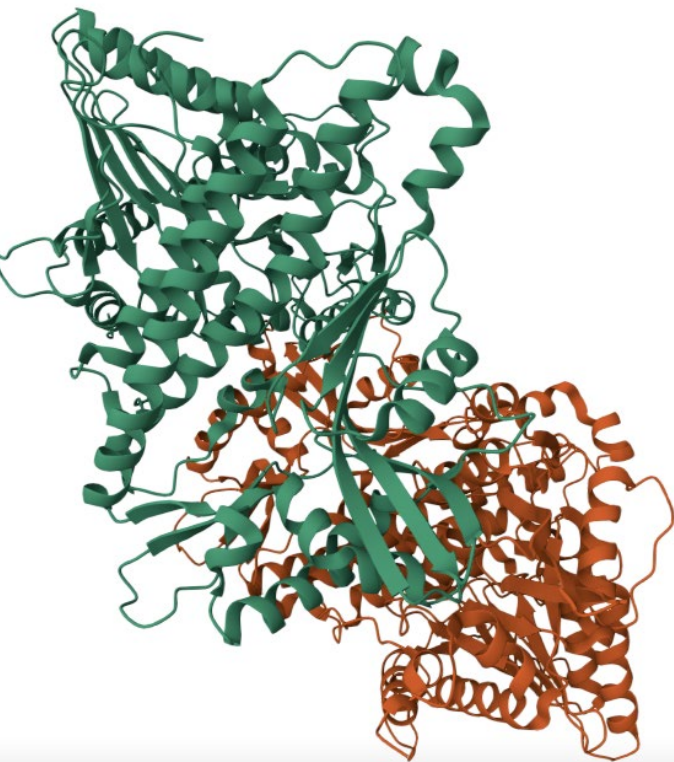
Dr Grumelli found that the LPS caused a strong immune reaction in the lungs, with high numbers of inflammatory cells that released enzymes and damaged tissues, this led to the breakdown of the alveoli and made the lungs less elastic.

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Targeting the bacterial enzymes that respond to choline, or changing the nutrients available in the lungs could reduce the severity of infections and improve patient outcomes.

Gas exchange in alveoli





△ Polyphosphate kinase.

They also discovered that choline made breathing much harder, the lungs had to use more energy and oxygen to function causing carbon dioxide to build up and acidify the blood. Interestingly, the team also found that choline doesn't just affect the lungs it also changes the bacteria, exposure to choline caused *P. aeruginosa* in the lab test to produce more LPS which would allow it to stick to and damage lung tissues. It also caused the bacteria to reduce its energy needs giving it a survival advantage in the lung.

Polyphosphate Production

These findings suggested that treating people with *P. aeruginosa* lung infections with succinate, may reduce the symptoms associated with choline and make the infections easier to treat. To understand more about how choline impacts *P. aeruginosa* in lung infections the team in Argentina expanded on their previous experiments and grew the bacteria in the lab using choline as its main energy source and compared it to bacteria grown with succinate.

Dr Grumelli discovered that choline caused the bacteria to switch into a survival mode, building up large amounts of a compound called polyphosphate which helps bacteria handle stress, resist attack by the body's immune systems, and be able to persist in the lungs for longer periods of time. They also found that an enzyme called polyphosphate kinase was much more active in the choline fed bacteria, while the enzyme polyphosphate phosphatase, which breaks down the polyphosphate, became less active. This resulting in the bacteria being able to build up large stores of polyphosphates and produce more LPS.

The laboratory tests showed that the bacteria grown with choline made less energy, but this allowed them to become more efficient. As they used less oxygen, they were also more able to survive in the low oxygen environment found within damaged lungs.

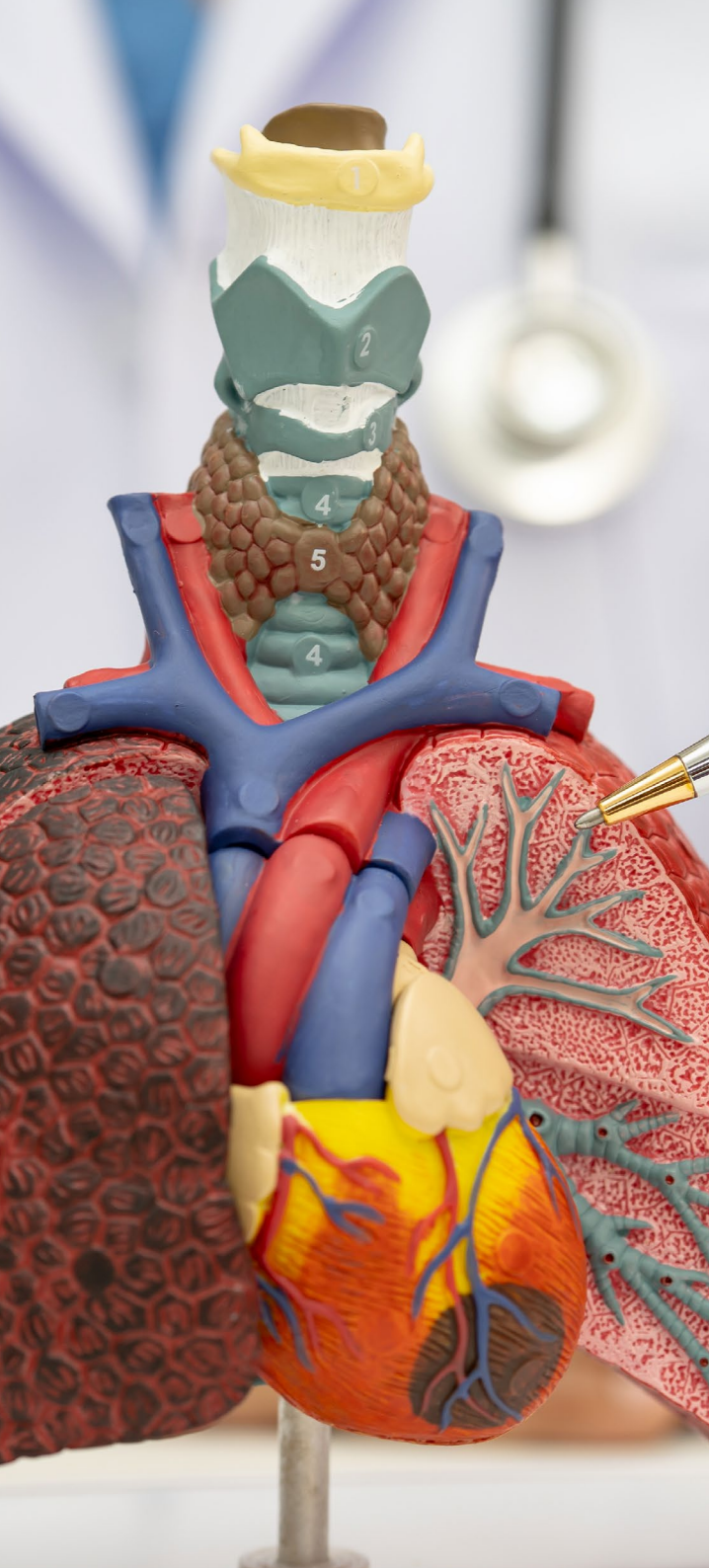
What This Research Could Mean for Patients

Dr Grumelli's work provides exciting insights into why *P. aeruginosa* infections are so difficult to manage in people with chronic lung conditions such as COPD and cystic fibrosis. Their work reveals that choline, a molecule naturally found in our lungs, plays a surprising double role as it not only makes breathing harder for patients during flare ups, but it also helps the bacteria survive and cause more damage.

This research highlights the potential for possible new treatment strategies. For example, targeting the bacterial enzymes that respond to choline, or changing the nutrients available in the lungs could reduce the severity of infections and improve patient outcomes. Dr Grumelli's findings may lead to therapies that go beyond antibiotics and support people living with chronic hard to treat lung infections.



Article written by Helen Rickard, PhD



MEET THE RESEARCHER

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Dr Sandra Grumelli is a biomedical scientist with over two decades of experience in respiratory research, translational science, and immunology. She obtained her PhD in Biology from the National University of Río Cuarto in Argentina, followed by extensive postdoctoral training at leading institutions including Baylor College of Medicine and Harvard Medical School. Her research has focused on chronic lung diseases, particularly the immune and metabolic interactions between *Pseudomonas aeruginosa* and the human host in cystic fibrosis and COPD. Dr Grumelli has held research and teaching appointments in Argentina and the USA, led projects funded by Tufts University and the American Thoracic Society, and received multiple international fellowships and travel awards. Dr Grumelli is also a science communicator, peer reviewer for leading journals including PLOS ONE and FEMS, and currently serves as an editor for The Journal of Disease. She combines her scientific background with certified training in medical interpretation to help bridge communication in clinical and research settings.

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FURTHER READING

S Grumelli, Choline Triggers Exacerbations of Chronic Obstructive Pulmonary Disease in Patients Infected with *Pseudomonas aeruginosa*, Current Respiratory Medicine Review, 2016, 12(2) 167-174. DOI: <https://doi.org/10.2174/1573398X12999160506104327>

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