



Lung injury: Inflammatory response in lung alveoli infected with *Pseudomonas aeruginosa*.

Supplemental solutions

The idea of treating asthma with nutritional supplements might seem unusual, but at least two clinical trials are testing this idea. Just a few years ago, an Australian group reported that individuals with severe asthma also tend to have a diet characterized by low fiber intake (5 g a day lower on average) when compared to healthy controls⁸. The same group recently led a small, 17-person trial in which researchers gave volunteers with asthma concentrated dietary fiber in a formulation known as inulin. The results, as measured by an asthma-control questionnaire, suggested that inulin improved asthma symptoms by a statistical significance. Lisa Wood, the principal investigator of the trial at Newcastle University in Australia, says that she and her team are currently planning a larger trial to determine whether the effects observed in their small trial are reproducible at a larger scale. She adds that her team also observed an increase in numbers of a beneficial bacteria called *Bifidobacterium* in the guts of trial participants.

Research suggests that nutritional supplements such as inulin work to boost the growth of gut flora, especially *Bifidobacterium*, that are thought to play a part in immune regulation. Neil Williams, an exercise and nutrition researcher at Nottingham Trent University in the UK, is launching a trial to test a commercially available prebiotic that helps to nurture the growth of *Bifidobacterium* in the human gut. The prebiotic, known as Bimuno Prebiotic Powder, will be given for a period of four weeks to 20 people who have exercise-induced asthma. The powder is made up of

carbohydrates called galacto-oligosaccharides, which are nondigestible in humans but similar to dietary fiber, according to Williams. The trial is awaiting clearance from an ethics board. Williams says that his team will look for any changes in the volunteers' asthma conditions, as well as changes to their gut-microbiome profiles and lung-inflammatory conditions (such as cytokine levels). Over time, asthma medication loses its efficacy, Williams says, and so addressing the underlying inflammation that causes asthma, potentially with the use of a prebiotic, could give patients with asthma a better shot at relief.

Studying the gut-lung axis might offer a way for pneumonia and asthma researchers to get a closer look at how the adaptive and innate immune responses come together to tackle lung disease. Unpublished research from Dickson's lab suggests that in healthy mice, levels of the cytokine interleukin-4, which aids in the differentiation of T_H2 cells in the adaptive immune system, reflect the diversity of bacteria in both the lung and the gut. This finding thus suggests that the adaptive immune system is influenced by bacteria in both organs.

In another study that demonstrated how innate immunity could play a part in combatting lung infections, Guery's group showed that the secretion of T_H17 cytokines by innate lymphoid cells was protective against pneumonia in cases where pneumonia infection occurred in the presence of other pathogens, namely, *Candida albicans*. His group colonized the lungs of mice with *C. albicans* and then exposed them to *P. aeruginosa*. Their findings showed a reduction in lung inflammation when compared to

control mice that were given a saline solution only and then exposed to *P. aeruginosa*. This protective effect was no longer observed in mice that were treated with an anti-fungal targeting *C. albicans*⁹. A follow-up analysis attributed this effect to the production of cytokines such as interleukin-22, which recruits natural killer cells, dendritic cells, innate lymphoid cells and macrophages to kill *P. aeruginosa* instead of *C. albicans*¹⁰.

Commercial companies are now beginning to set up programs of their own to investigate the therapeutic potential of manipulating the gut-lung axis. Nestlé told *Nature Medicine* that the company is conducting research into which dietary supplements could be used as interventions for allergies. Boston-based start-up Commense is also exploring the creation of a probiotic to administer to children that might help to prevent the development of asthma, although no trials have yet been initiated.

Both these programs are nascent, and so any novel therapeutic interventions for disorders of the gut-lung axis may still be years away. But researchers who are interrogating the connection between the gut and the lung are excited about the prospect of more options for patients in need. Especially for those in the ICU who have few antibiotic options readily available, "we need to develop alternate therapeutics," Guery says. The kinds of studies that are now being conducted "could give you a rationale to try something new in the clinic," he adds.

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Correction

In the March 2017 issue, the piece "A protein puzzle: Untangling the mysterious condition of amyloidosis" (*Nat. Med.* **23**, 266–269, 2017) incorrectly stated that the FDA placed Ionis' NEURO-TTR trial on hold. The FDA had placed a related trial called CARDIO-TTR on hold after some patients in the NEURO-TTR trial developed complications. The error has been corrected in the HTML and PDF versions of this article.