Mr Rohan Kubba

E: rohan.kubba12079@cnsu.edu

Nivolumab against lung cancer: How is the gut–lung axis involved?

Research Objectives

The researchers shed light on the relationship between the use of nivolumab and the resulting changes of the species populating the bowel of lung cancer patients.

References

- Kubba, R, Evans, RJ, Nguyen, S, et al, (2023) Effect of nivolumab therapy on metastatic lung cancer in human microbiome. [preprint] *BioRxiv* [online]. doi.org/10.1101/2023.01.03.522679
- Chen, J, Li, T, Ye, C, et al, (2023) The lung microbiome: A new frontier for lung and brain disease. *Int J Mol Sci*, 24(3), 2170. doi.org/10.3390/ijms24032170
- Tsay, JJ, Wu, BG, Badri, MH, et al, (2018) Airway microbiota is associated with upregulation of the PI3K pathway in lung cancer. *Am J Resp Crit Care Med*, 198(9), 1188–1198. doi.org/10.1164/rccm.201710-2118oc

CALIFORNIA NORTHSTATE UNIVERSITY
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Detail

Bio

Rohan Kubba was born and raised in Southern California and attended UCLA for his bachelor's degree in biology. He is currently enrolled as a medical student at California Northstate University.

Personal Response

What current technologies and techniques could be used to further investigate the interactions of the gut microbiota and the immunotherapy medicines on a molecular level? What would the next study looking closer at these involve?

" Using more robust analyses, like shotgun sequencing, can give us a more nuanced view of a person's total microbiome. Specifically, because of shotgun sequencing's ability to include nonbacterial fungi and viruses in single analyses, their effect in human health and disease are magnified. While immunotherapy is a vital component to cancer treatment among other therapies, exploring the gut microbiome in relation to all diseases, and specifically chronic diseases like diabetes, is warranted. Future studies should evaluate the effectiveness of localised bacteriophage therapy to potentially control overabundant pathogenic microbiota. "

Nivolumab against lung cancer

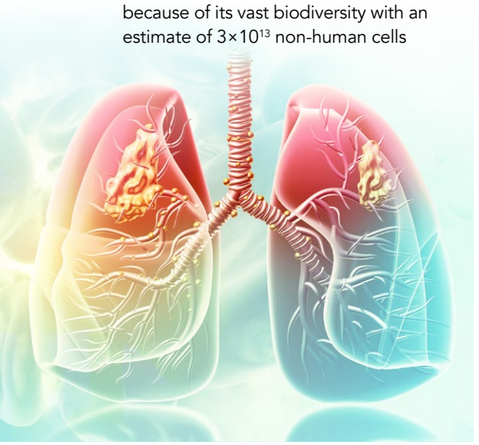
How is the gut–lung axis involved?

The study of the gut microbiome, which is the total of all the microbes living in the intestines, has been shown to not only play an important role in the health of the bowel itself, but also in the health of distant organs such as the lungs. Lung cancer is one of the diseases that is often difficult to treat successfully. Rohan Kubba from the California Northstate University, Elk Grove, USA, believes that by studying the gut microbiome he can understand more about how anti-cancer treatments affect the gut–lung axis, and how the variations found in patient microbe populations are associated with treatment outcomes.

The microbiome consists of thousands of species including bacteria, fungi, and viruses (microbiota). Each person has an entirely unique network of microbiota, most of them living in their gut but also on the skin, mouth, and lungs. Each person's microbiome is formed by a combination of factors, including but not limited to exposure to microorganisms during natural birth, consuming their mother's milk, and later on in life, environmental factors such as diet.

GUT MICROBIOME AND DISEASE

The gut microbiome, more specifically, has been the focus of microbiome research over the past years, mainly because of its vast biodiversity with an estimate of 3×10^{13} non-human cells residing inside the human bowels – a number higher than the number of cells that make up the entire human body!



The relationship between the gut microbiota and humans is not just one of a peaceful coexistence, it is also an interdependent relationship. Many of these microbes protect us against harmful bacteria, synthesise certain nutrients, support the immune system, and enable the body to digest food. For this to work well, there needs to be a complex balance between the different species that comprise the microbiome.

This balance can be disturbed by factors such as diet, geography, and stress among other factors and, if imbalanced for an extended period, can lead to disease. By studying the healthy microbiome as well as the microbiome at the time of disease, researchers are aiming to better understand the interaction of the human body with its microbiota, and how any population changes caused by medicines such as antibiotics and other factors can affect the development and course of disease.

At the University of California, Riverside, USA, Rohan Kubba has collaborated with fellow researchers to study the gut microbiome so they can understand more about how anti-cancer treatments affect the gut–lung axis.

THE GUT–LUNG AXIS

Besides affecting the bowel itself, gut microbiota dysbiosis can also affect distant organs such as the lungs. Until recently, it was believed that the lungs are a sterile environment. Now we know that although less populated than the gut, the lung has its own distinct microbiome, which includes microorganisms that are in abundance in the intestines. The composition of the lung microbiome depends on the microbes that mainly come from the oral cavity, the pharynx, and the upper respiratory tract, and is affected by the pH, the smoking status, and other environmental factors.

The gut–lung axis is a system of communication between the bowel and the lungs which explains how changes and imbalance in the gut microbiome may affect the health of the lungs, either through microorganism migration that directly alters the lung microbiome, or by sending signals to the lungs via the lymphatic system – the specialised vessels and organs whose main function is the circulation of immune cells and the return of fluids from the tissues into the bloodstream. This communication suggests that the gut microbiome could be reflecting the lung health status and potentially also serve as a diagnostic marker for lung disease.

These signals can be small inflammation molecules such as cytokines, released by the immune cells of the bowel, or biochemical compounds produced by the microorganisms themselves. They eventually cause changes in the lungs along with persistent physical irritation that can lead to the development of diseases such as chronic obstructive pulmonary disease (COPD), asthma, and lung cancer.

Recent studies on the lung microbiome have shown a connection between variations in the population of microorganisms and changes in lung epithelial (inner lining) cells associated with the development of lung cancer (carcinogenesis). More specifically, in patients with lung cancer, the lower airways were found to have higher abundances of microbial populations that can lead to oral disease as well.

The presence of these microorganisms was also corresponding to changes in certain molecular processes inside the epithelial cells that were previously found to be related to lung cancer development. One such process is the phosphoinositide 3-kinase (PI3K) pathway. PI3K-Akt is a specific PI3K signalling pathway that regulates cell proliferation and cell survival, and is usually found to have higher activity in cancerous cells for prolonged survival.

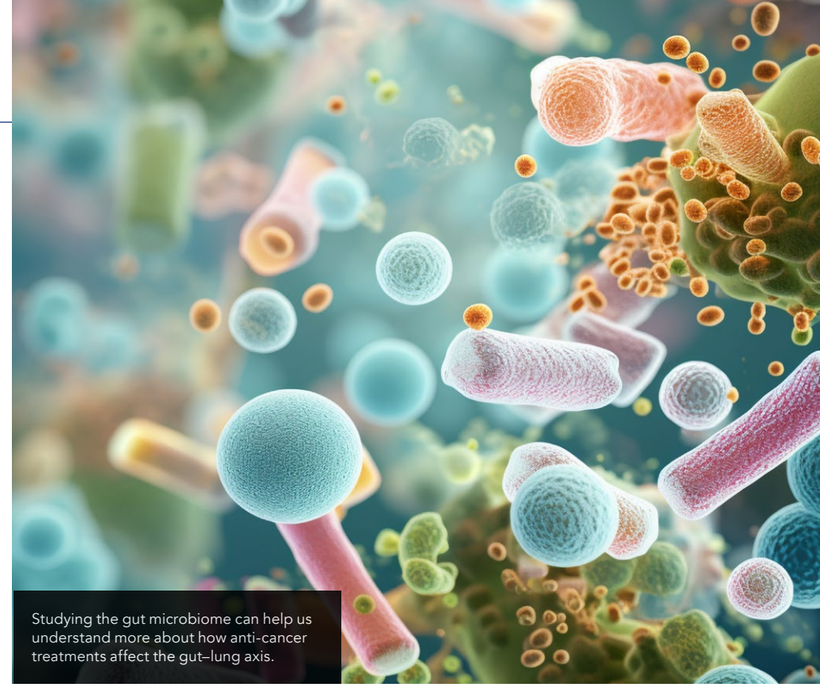
WHAT IS NIVOLUMAB?

Nivolumab is an immunotherapy drug, which means it enables the body's defence mechanisms to fight off cancer cells. It is currently used to treat several types of cancers, including lung cancer, renal cancer, and melanoma. Nivolumab works by blocking the action of the PD1 receptor on cytotoxic T cells. In this way, the drug allows the immune cells to accurately detect and effectively kill cancer cells.

It is not entirely clear yet how nivolumab affects the gut microbiome. Previous studies investigating how this drug affects the gut microbiome in cancer patients show that there are significant differences in the abundance of certain microorganism populations before and after treatment. Kubba and fellow researchers decided to shed more light on the relationship between the use of nivolumab and the resulting changes of the species populating the bowel of lung cancer patients.

THE EXPERIMENT

The study involved five patients with advanced lung cancer to be started on nivolumab. Prior to the commencement of their treatment, all participants had to provide a stool sample. A second sample was then provided three months after nivolumab treatment.



Studying the gut microbiome can help us understand more about how anti-cancer treatments affect the gut–lung axis.

The relationship between the gut microbiota and humans is not just one of a peaceful coexistence, it is also an interdependent relationship.

All stool samples were analysed using 16S rRNA gene sequencing, a technique that helps map the presence of all the prokaryotes present in the sample and therefore, identify their species as well as their population numbers. The patients also underwent computer tomography scans (CT) for the measurement of their tumours before and after the treatment.

The results of the study showed that four out of five patients benefitted from the treatment, with their tumours remaining stable or shrinking over the three–month treatment period. Three of these were found to have a dramatic reduction in the population of a specific microorganism, the *Megasphaera elsdenii*, while the patient whose cancer did not respond to the treatment with nivolumab had a seemingly unstable imbalanced gut with drastic changes over the span of three months. The results were statistically analysed and revealed a significant association of the effectiveness of nivolumab against cancer and reductions of the lung population of *Megasphaera elsdenii*.

WHAT DID THE MICROBES SAY?

Megasphaera elsdenii is a bacterium responsible for breaking down carbohydrates the human body cannot otherwise digest by producing butyrate, (among other metabolites), a molecule that can be used as energy source in the bowel and also boosts the body's immune system. In other tumour types including pancreatic and colorectal cancers, the increase of *Megasphaera elsdeniiis* population in the tumours was found to correlate with favourable outcomes for the patients; however, the findings of this study suggested an opposite effect.

A possible reason behind these contradicting findings could be that different types of cancer may behave differently on a microscopic level and therefore, the different treatments used against them may also have contrasting effects on the gut microbiome. Further studies involving more participants could potentially provide more information and build the road towards making microbiome changes a prognostic tool for cancer outcomes.

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