# The imbalance of the complement system in lung cancer patients

*Researchers can detect cancer developing in patients by measuring certain proteins known to behave in a certain way. However, complement proteins in our immune system behave in a way that is not consistent; complement proteins are higher in blood but lower in cancer tissue from lung cancer patients who have been given a negative prognosis. Professor Muying Ying, based at the Basic Medical College of Nanchang University, wants to solve the mystery behind these strange results and potentially develop a new marker to detect lung cancer.*

Our immune system is vital for our survival. Without it, we would get sick from every bacteria, virus, or parasite that came our way. A vast network of tissues and cells are constantly in surveillance mode, looking out for invaders and, if there is an attack, mobilising the body's defences.

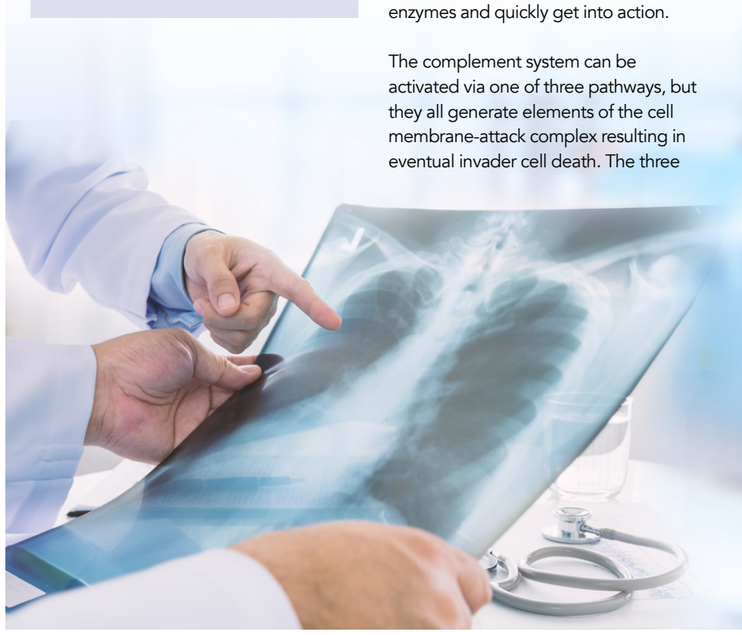
The complement system, participating in both innate immunity and adaptive immunity, is a very important part of our immune system. It works as an add-on to the main immune system, to enhance its ability to attack and clear any invading microbes. It consists of a series of small proteins, which circulate in the blood in their inactive form. If there's a call-out, they're activated through specific enzymes and quickly get into action.

The complement system can be activated via one of three pathways, but they all generate elements of the cell membrane-attack complex resulting in eventual invader cell death. The three pathways are composed of a series of complement members which are present in the blood in inactive precursor forms. The initial attack triggers activation of the first element followed by a cascade amplification effect in the signal transduction pathway.

Crucially, the complement system not only recognises foreign bodies, such as bacteria, but it can also spot and destroy dead and faulty cells. Cancer cells are one such example. In this context, the complement system is paradoxically both against and in favour of cancer development: on the one hand, it can block tumour growth by promoting an acute inflammatory response; on the other hand, it stimulates growth by triggering a chronic inflammatory response.

As a result of this discrepancy, previous studies looking at the levels of various elements of the complement system in patients suffering from lung cancer also reveal a paradox. In some cases, elevated levels of complement components are associated with a poor prognosis, but at the same time, patients with low levels of complement components face the same scenario.

Keen to solve this mystery, Professor Ying combined a review of past studies looking at the complement system with a more in-depth analysis of patients suffering from lung cancer. For the researchers, understanding how the complement system reacts to the presence of cancer cells may be the key to developing a new diagnostic tool or therapeutic approach to treat these patients.



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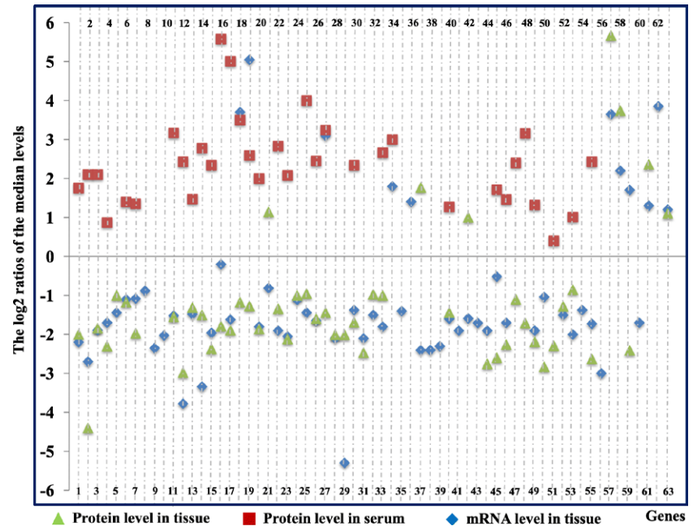



Expression profiles of complement and complement-related components in serum and cancer tissues from patients with lung cancer. The levels of the proteins in the serum are much higher than those in the tissue. Originally published in *BMC Cancer*: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5422-x under CC BY 4.0.

## COMPLEMENT PARADOX

The team started their analysis with all available previous studies, comparing the levels of about 40 known complement components in patients with lung cancer. From this general data, it turned out that levels decreased in cancer tissues, but increased in the bloodstream, creating a somewhat lopsided and imbalanced complement system.

These results caught Prof Ying by surprise, and further questions for research were developed: "Do lung cancer patients often have an imbalanced complement system characterised by decreased levels of complement components in lung cancer tissues but increased blood concentrations of complement proteins? What is the possible physiological mechanism behind this imbalance?"

To answer these questions, the team turned to lung cancer patients to analyse how the various elements of the complement system behave in real conditions. The results were the same: low levels in lung cancer tissue but high levels in the blood from lung cancer patients. A member of Prof Ying's team explains: "To date, this study represents the most comprehensive analysis of the imbalance in the complement system in patients with lung cancer from the epidemiological perspective."

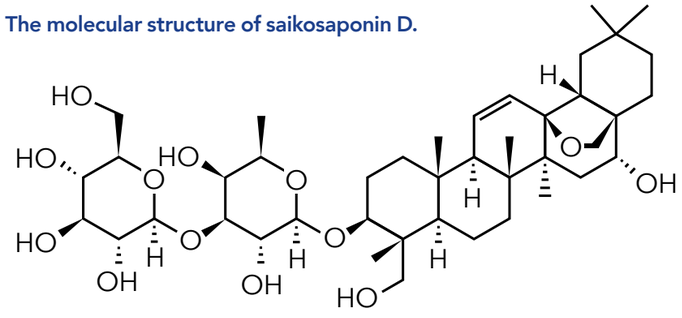
***Prof Ying's team turned to lung cancer patients to analyse how the various elements of the complement system behave in real conditions.***

Prof Ying speculated that, as a response to the drop in lung cancer tissue, the body overreacts and promotes secretion of elements of the complement system to replenish the lost complement components. In practical terms, the body reacts to the low levels of complement components in lung cancer tissue by stimulating production of the complement components in the liver. The liver is, after all, the major organ involved in the immune system and controls the synthesis and secretion of many critical blood constituents to maintain a balance in the bloodstream.

In addition, it may be possible to use this paradoxical mechanism as a marker. It's not unreasonable to suggest that the imbalanced complement system between lung cancer tissue and the blood of patients can be seen as a sign to detect early cases of lung cancer.

Complement components are mainly synthesised and secreted by hepatocytes (liver cells). "As a dynamic window of insight into the physiological and pathophysiological status of patients with lung cancer, the changes of complement synthesis and secretion in the hepatocyte

**The molecular structure of saikosaponin D.**



Sickle-leaved hare's ear is widely used throughout Asia as a medicinal plant.

***The drug shows serious promise as a potential treatment for lung cancer patients, and one with minimal side effects.***

may be important to monitor system-wide responses to the onset and development of lung cancer," says Prof Ying.

For Prof Ying, this is only the beginning of the journey. Possible links between this disrupted complement system and other types of cancer remain unresolved. The complement system probably has many functions that are yet to be discovered, including immune response, clearing immune complexes, the migration and invasion of cancer cells and tumour angiogenesis (blood supply) – its importance cannot be ignored.

**ANOTHER CONUNDRUM**

Curiously, this is not the only conundrum of positive/negative effects that Prof Ying's team has had to solve. A drug originating from a plant commonly known as sickle-leaved hare's ear *(Bupleurum falcatum L.)* also showed a positive effect on the death of cells (apoptosis), but a negative effect on cell proliferation in lung cells cultured *in vitro*.

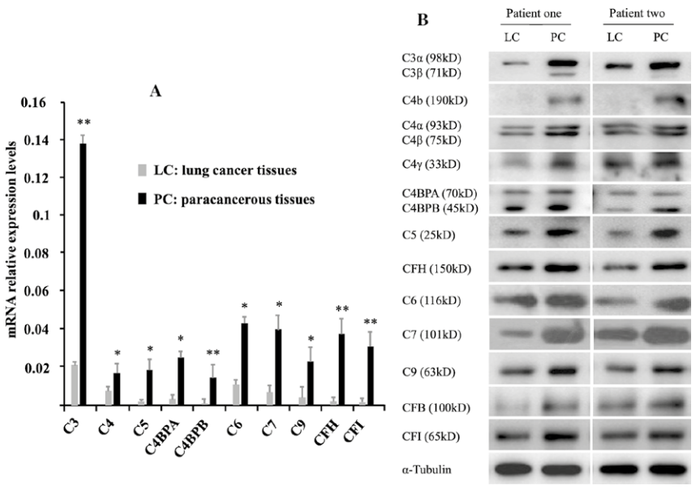
This plant is widely used among people in Asia to treat respiratory infections, including the flu, the common cold, bronchitis, and pneumonia, as well as digestive problems such as indigestion and constipation. Researchers have identified the active ingredient as saikosaponins, of which version D is the most potent of 11 different types.

For Prof Ying and her team, one of the most interesting and potentially useful applications of saponin D is to treat lung cancer patients. To find out how saponin D acts on lung cancer cells, the team cultured human lung tumour cells in the presence of the drug and measured 18 key proteins regulating cell cycle, apoptosis and proliferation.

Surprisingly, saponin D increased expression of the 18 key proteins, including the positive and negative regulators of the cell cycle. The negative regulatory proteins of the cell cycle have a negative effect on cell growth (and thus prevent tumour growth). The positive regulatory proteins have a positive effect on cell proliferation (and thus promote tumour growth). In the team's results, the presence of saponin D resulted in an increase in the *prevention* of tumour growth, thus showing great potential to limit the survival rate of lung cancer cells. Prof Ying believes this drug shows serious promise as a potential treatment for lung cancer patients, and one with minimal side effects.

What's more, these effects can be further enhanced by adding a second drug into the mix. It turned out that combining saponin D with another drug SP600125 had a synergistic effect on inhibiting cell proliferation. In other words, the two drugs showed a combined effect greater than would be expected just by adding their separate effects.

Prof Ying explains, "Our study unveils previously uncharacterised synergistic actions, and provides a rationale for the combination of saponin D with SP600125 in the treatment of lung cancer."




Levels of complement components in lung cancer tissues (LC) and paracancerous tissues (PC) from two patients. Lower concentrations of complement components were observed in LC than in PC at the mRNA (a) and protein (b) levels. The mRNA levels of complement components C3, C4, C5, C4BPA, C4BPB, C6, C7, C9, CFH and CFI were decreased 6.4-, 2-, 11-, 8.6-, 64-, 4.5-, 5.5-, 7-, 9- and 13.5-fold in LC, respectively (a). α-Tubulin was used as the loading control (b). Data are presented as the means ± SD (n = 3). Originally published in *BMC Cancer*: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5422-x under CC BY 4.0.



# Behind the Research

## Professor Muying Ying

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## Research Objectives

Professor Ying is interested in understanding the roles of the imbalanced complement system in cancer growth and its early detection.

## Detail

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**Bio**

Professor Ying completed her PhD at the State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences in 2010. She spent a year at Stanford University School of Medicine in 2014, and was visiting scholar at the Medical Center of Erasmus University in 2015, before moving to Basic Medical College of Nanchang University where she currently holds a professorship.

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**Collaborators**

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- Zhao, P.
- Wu, J..
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- Zhou, N.

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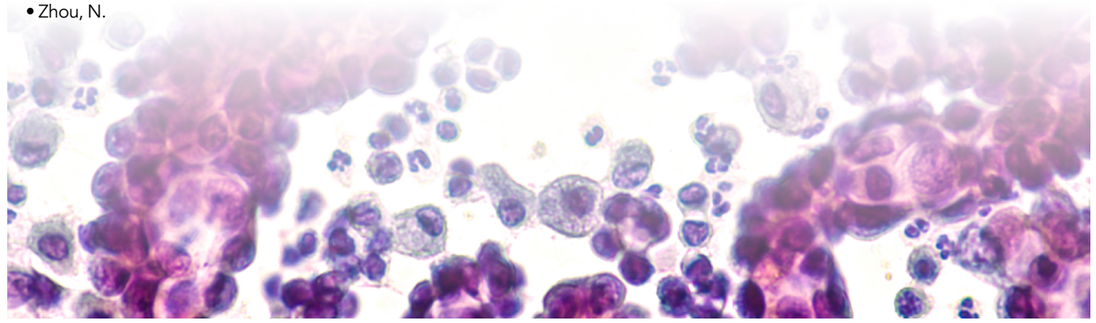
## Personal Response

***Do you think the complement system has similar functions in other types of cancer?***

"Sure, for decades, the complement system has been recognised as an effector arm of the immune system that destroys tumour cells. While it is true that the complement system demonstrates a tumour-promoting role in our recent study, cancer cells seem to be able to establish a balance between complement activation and inhibition, bug-using complement initiation without suffering its destructive effects."



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