The imbalance of the complement system in lung cancer patients

O ur 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 addition 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.

Kean 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.

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. 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, in return, recognises foreign bodies, not only recognises foreign bodies, but it can also spot and destroy dead and faulty cells.

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.

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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.”

References

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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