THE JUMPING GENE

AND THE SOLUBLE PROTEIN

Kevin Ng and colleagues are behind the discovery of a soluble protein produced by a "jumping gene" – an insertion of ancient parasitic DNA into the genome. The work has the potential to transform immunotherapy treatment and may also have therapeutic implications.

KEVIN NG

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In recent years, immunotherapy has transformed the way we think about cancer treatment. The type of therapy, which relies on the body's immune system to control and eliminate cancer, has the potential to radically transform the way the disease is managed in the future.

A lot of the interest has revolved in particular around the immune checkpoint protein *PD-L1*, which functions by keeping immune cells in check, making sure that healthy cells are not destroyed during the immune response. Cancer cells, however, have been shown to exploit this system to escape detection by immune cells. Blocking *PD-L1* with monoclonal antibodies has thus been used as a strategy to overcome cancer's ability to resist the immune response and to slow down the growth of tumours.

So far, however, the benefits of this therapeutic approach have only been seen in a number of patients. To move beyond this, more research is needed to learn more about *PD-L1*, the way it is produced and the way it functions, and this is exactly the type of work that Kevin Ng, a PhD student at the Francis Crick's Retroviral Immunology Laboratory and his colleagues have done. In a study published in *eLife*, they have identified a soluble form of the *PD-L1* protein produced by a gene, which has been altered by parasitic DNA – a so called "jumping gene".

Starting out

"When we started off this project, we had no idea that we would end up in the field of cancer. In fact, our interest revolved around "endogenous retroelements" – parasitic ancient DNA that can jump around the genome. We wanted to know more about how it can affect the function of genes. During the course of our research we discovered a specific retroelement embedded within the gene responsible for the production of *PD-L1*. Because it's a gene that is hugely important for immunotherapy, but also for auto-immunity, we decided to study it in detail," Kevin Ng, who is the lead author of the study, points out.

With his colleagues, he has also shown that the soluble form of the protein can play an important role in strengthening the immune response to fight off cancer cells. Indeed, their study shows that when the two forms of the *PD-L1* protein are present together, the soluble version outcompetes the normal version to bind to a common receptor used by both proteins. This process appears to block the action of the normal immune checkpoint protein *PD-L1*, preventing it from inhibiting immune T cells.

Below. 3D structures of full-length, transmembrane PD-L1 (left) and soluble PD-L1 (right). The PD-1 interacting domains are shown in blue, with differences between the two versions highlighted in red.

Questions raised

Because *PD-L1* is a protein that does not exist in the mouse genome, Kevin Ng and his team were restricted to studying human immune cells, isolated from the blood of healthy donors. "Any attempt to reconstitute an entire human immune system in a petri dish is challenging, so we decided to isolate relevant T-cells from blood samples and tested their activation in the presence of normal *PD-L1* and soluble *PD-L1*", Kevin Ng points out.

The team believes that the insertion of parasitic DNA into the genome, which led to the production of the soluble protein, occurred about 200 million years ago.

"The DNA for the soluble protein can be found in the genome of every individual, but whether it is produced depends on a number of factors that we are trying to figure out. We know the protein is expressed in both healthy and diseased individuals, and seems to be most highly expressed in certain organs, such as the lungs. Why is it expressed there, what is it doing and what happens if we take it away are all the questions we are looking to answer in the near future. We want to learn more about how it might contribute to normal immune function, and from that how it can help boost immunotherapy and how it's deregulated in autoimmune diseases," Kevin Ng says.

The potential

While these published results are still preliminary, there is much optimism that this work will help improve the management and treatment of a number of diseases, including cancer. "It might be too early to say exactly how this could be translated into immunotherapy. However, in recent years, there has been much interest in CAR-T cells, which are engineered T cells that can target tumours. One of our hypotheses is that we might be able to take CAR-T cells and make them express the soluble form of the protein, which might help potentiate the immune response," the researcher explains.

Another area of interest for the team is the field of autoimmune diseases, such as type 1 diabetes and multiple sclerosis. In the coming years, their aim is to study how soluble *PD-L1* might be regulated in autoimmune diseases. They hope that the results of their investigations can give them new leads in the development of new treatments for patients. "If we reach this point, we might even look to see if we can repurpose any of the drugs that are already in the clinic for cancer to test whether they can be of help in the treatment of autoimmune diseases," Kevin Ng concludes.