Aging immune system may explain age-related cancer risk increase

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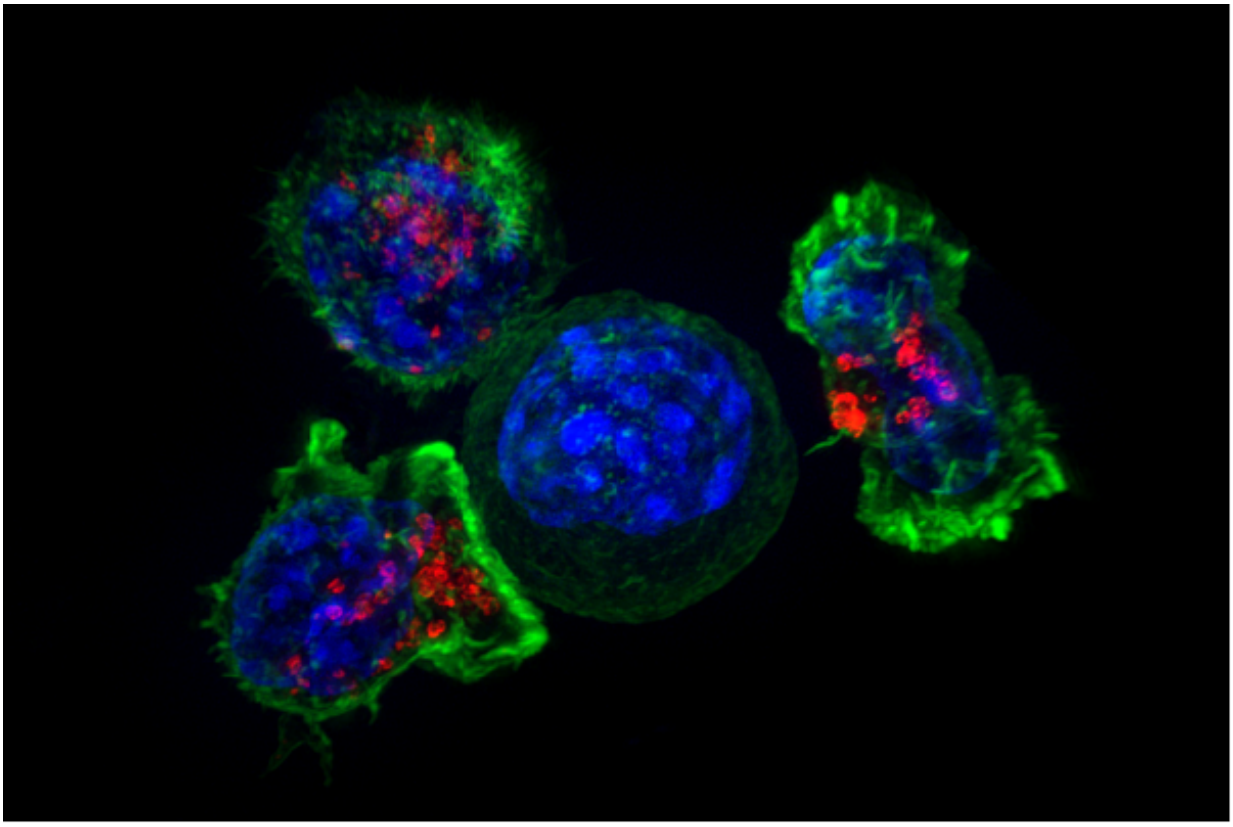

Killer T cells surround a cancer cell. Credit: NIH

Study published in *Proceedings of the National Academy of Sciences* suggests aging immune system plays a larger role in cancer incidence than previously thought. Findings may explain higher likelihood of men

developing cancer than women. This epidemiological research could have major implications for global fight against cancer if borne out by further studies.

The key to cancer prevention may lie in the immune system rather than genetic mutations, the current focus of most anti-cancer efforts across the world, according to a major new study carried out at the University of Dundee.

Eight million people die of cancer across the world each year. Men are significantly more likely than women to be diagnosed with cancer in their lifetime, and for most cancers the chance of developing the disease rises dramatically with age.

For decades, it has been known that mutations arising either as a result of genetic predisposition, or lifestyle and environmental factors cause cancer. The traditional view is that the way cancer incidence increases with age could be understood and quantified if multiple (typically five to six) mutations in one cell are required to initiate cancer.

The Dundee team, which also features researchers from Heriot Watt University, the University of Edinburgh and the Institut Curie in France, have shown that the declining immune system with age may actually be a stronger reason for the increasing incidence of developing cancer than multiple mutations.

Following the hypothesis that an ageing immune system may result in higher rates of cancer, just as it leads to older people being more prone to other diseases, they looked at data on 2 million cases of cancer over the 18-70 age range. They then developed a mathematical equation for how they would expect cancer incidence to rise in relation to a declining immune system and compared it to the age profiles for 100 different cancers.

Their model fitted the data better than the multiple mutation hypothesis. Because the immune system generally declines more slowly in women than men, they were also able to account for the gender difference in cancer incidence, something that mutations alone cannot easily explain.

This suggests that the immune system, particularly as it declines, may play a far bigger role in the development of cancer than previously thought. If borne out by further studies, this could have significant implications for cancer prevention and treatment across the globe.

"This is still very early days but if we are proven right then you could be talking about a whole new way to treat and prevent cancer," said senior author Dr Thea Newman, formerly Vice Principal of Research and Professor of Biophysics and Systems Biology at Dundee.

"Nearly all of the mainstream research into cancer is based on how we can understand genetic mutations, target them and thereby cure the disease. We're not debating the fact that mutations cause cancer, but are asking whether mutations alone can account for the rapid rise in cancer incidence with age when ageing causes other profound changes in the body."

A primary cause of immune system ageing is the shrinking of the thymus gland. This is where T cells, which circulate the body killing dysfunctional cells or foreign agents, are produced.

Thymic involution begins from around the age of one and the thymus roughly halves in size every 16 years, with a corresponding fall in the production of T cells. The researchers found an extremely strong correlation between the chances of certain cancers increasing and the new T cell populations falling.

"The immunosurveillance hypothesis is that cancer cells are continually

arising in the body but that normally the immune system kills them before a new tumour is able to establish itself," said Dr Sam Palmer, who initiated the research at Dundee before taking a post at Heriot Watt University.

"The T cells are constantly scanning for cancer cells, looking to destroy them. If they can't find them soon enough or the immune system is weak then the cancer population has the chance to grow. The chances of this happening will increase with age as the thymus is shrinking all the time.

"For our model, we imagined a war between T cells and cancer cells, which the cancer cells win if they grow beyond a certain threshold. We then set this threshold to be declining with age, proportional to T cell production. This simple hypothesis turns out to be able to explain much of the cancer incidence data."

Dr Luca Albergante, formerly of Dundee and now based at the Institut Curie, added, "The increase of cancer incidence with age is slower in women, something which we would naively expect to be effectively gender-neutral. However, the thymus gland shrinks more slowly in women, so we were able to make a prediction on the differential cancer incidence with gender that once again shows our model to be more accurate than the traditional model."

The team tested their model on data from the US-based National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme. The results showed that many cancers appear to be very strongly linked to the decline of the immune system, while others are more likely linked to a combination of immune system decline and multiple mutations.

Professor Clare Blackburn of the University of Edinburgh, an expert in thymus biology, said, "We believe that our findings are extremely

relevant and show the need to take the immune system even more seriously in cancer research.

"In addition to mutations, this suggests we should also focus on how to boost thymus function in a controlled way, perhaps by transplantation or by controlled regeneration, so we can increase the number of T cells we are making. Of course, we also need to look at whether there may be unintended consequences of doing this, and how to minimise these if they occur."

More information: Sam Palmer el al., "Thymic involution and rising disease incidence with age," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1714478115

Provided by University of Dundee