Unlocking the secrets of the immune cells: The key to preventing cancer later in life?

Details

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Bio
Yuri Sykulev received his MD and PhD degrees from Pirogov Russian National Research Medical University. His interest lies in virus- and cancer-specific cytotoxic T lymphocytes (CTL), and he has made significant contributions to understanding the mechanisms regulating the functioning of CTLs, which can be used to engineer highly efficient T cells for immunotherapeutic interventions.

Further reading

Address
Departments of Microbiology and Immunology and Medical Oncology, Sidney
Unlocking the secrets of the immune cells
The key to preventing cancer later in life?

- Cancer is a disease associated with older age.
- This might be because our immune cells change as we age.
- Studying these changes could give us more information about how and when cancer develops.
- Dr Yuri Sykulev at Thomas Jefferson University, USA has invented a method to study a small number of immune cells in conditions mimicking their natural environment.
- His research could help us identify cancers early enough to treat them.

Despite the ongoing development of new, sophisticated treatments that increase patient survival, cancer remains the second leading cause of death, after heart disease. With the world's population becoming older, this public health problem is more prevalent than ever. It is estimated that more than 60% of new cancers present in people older than 65 years. Studying the cellular and molecular changes that come as we age could help us understand what mechanisms make us more vulnerable to cancer and infections later in life. Identifying these changes in a timely manner helps us to prevent them from leading to disease.

Cancer and the immune system
When the cell DNA is being copied during cell division, mistakes called mutations can occur that may lead to damaged cells. Most of the time, our body repairs these mutations, but as we age there's more time for mistakes and the consequent cell damage to build up. Over time, this damage may lead to cancer. As well as these ever-accumulating mutations, other factors contribute to the appearance of cancer, including changes to our immune cells.

The cells of the immune system – called T lymphocytes or T cells – protect tissues from the manifestation of malignant tumours. T cells can recognise tumour-associated antigen through receptors on their surface, and initiate T cell attack to fight cancer. Recently, it has been shown that ageing of the immune cells might play a more important role than the ageing of any other cells – as accumulation of damaging changes makes them unable to protect our body and prevent cancer.

These changes have been observed in immature T cells, called naïve T cells, and they are present in both the circulating blood and the body's lymph tissues. Most experimentally used T cells come from blood T cells, and represent only a small fraction of the body's T cell population. To achieve a more comprehensive understanding of how T cells work in their actual environment, Dr Yuri Sykulev at Thomas Jefferson University in

T cells showed signs of an abnormal early maturation, which could explain why we are more likely to be affected by cancer as we age.

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the USA developed a new technique that simulates the cell membrane of targeted cells. This allows a small number of T cells taken from peripheral blood to be exposed to the cell membrane and then studied in a realistic setting.

**Simulating the cell membrane**

Sykulev and his collaborators created a model of the double-lipid cell membrane – the membrane surrounding cells that allows only specific molecules to be presented at the membrane. To achieve this, they used microscope slides, small squares of clear glass built into plastic chambers. On the slides, they built lipid bilayers (a double layer of lipids with the water-friendly sides facing out and the fat-friendly sides facing the supporting glass) containing molecules that interact with the T cells. This model enables experimentation on T cells in a more tissue-like environment, especially since it simulates how T cells interact with tissue leading to T cell activation followed by the release of toxic granules (cytolytic) that kill aberrant cells.

**This could be the first step in exploring a new type of T cell prognostic cancer marker, which may help us identify early changes and prevent cancer from developing.**

The researchers applied T cells to the model membrane containing fluorescent-labelled antigens, which bound to the T cell receptors. This allowed them to visualise the T cell-membrane interface with two special microscopes: confocal, and total internal reflection fluorescence (TIRF) microscopes. The interface structures mediated by the ligand and T cell receptor interactions were examined and four different types of T cells were identified. The release pattern of cytolytic granules and formation of specialised interfaces (synapses) were used as an indicator of cell maturation and the quality of their response.

**Putting the theory to the test**

Dysfunctional T cells that cannot control the development of tumours (tumorigenesis) are thought to be very similar to those seen in patients with long-standing HIV infection. In these cases, T cells are unable to contain the virus and prevent the disease. Sykulev and his team wanted to test their hypothesis that ageing is a progressive degenerative process tightly associated with inflammation – the complex biological response of our body to harmful agent. To do this, they carried out a study on T cells from individuals that had been affected with HIV for years. Their aim was to investigate whether ongoing inflammation leads to damaged naïve T cells, which, in turn, would make us more susceptible to cancer as we age. Using their new method of simulating the cell membrane, they demonstrated that individuals chronically affected with HIV had a higher number of aberrant naïve T cells compared to healthy individuals.

**Personal response**

Was there any finding that particularly surprised you when you applied your new method of studying tissue T lymphocytes to tissues from HIV patients?

We were surprised to find that a substantial fraction of naïve T cells derived from people chronically infected with HIV were capable of forming peripheral ring junctions, similar to that found in activated T cells.

How are your findings potentially going to affect future diagnostic and prognostic techniques? Do you already have any applications in mind?

Analysis of the structure and dynamics of the synaptic interface, as well as patterns of Ca2+ mobilisation and granule release could serve as prognostic factors predicting the quality of T cell response.

What is the next research project planned by your team?

We plan to analyse the structure of the synaptic interface of naïve T cells derived from young and ageing people, including those developing cancer.

These prematurely ageing naïve T cells can create synapses similar to activated T cells, a sign of an abnormal early maturation. This process partially explains how the immune system wears out with age, making it more likely for us to be affected by cancer later in life.

The successful experimentation on the lipid bilayer membrane model means that their method could also potentially be used directly on the tissues and therefore help identify specific cell features that have been so far less studied compared to others.

Today, it’s thought that ageing of the immune system could be responsible for the higher cancer rates seen in older age, rather than the accumulation of DNA mutations. This ageing is especially relevant for specific subtypes of immune cells such as the naïve CD8+ T cells (that can develop into so-called effector T cells capable of killing other cells, such as cancer cells). The team’s new method, besides reducing the number of cells and reagents required compared to traditional techniques of studying T cells, has also shed some more light on the behaviour and structure of our ageing immune cells. These findings make the researchers hopeful that this could be the first step in exploring a new type of T cell prognostic cancer marker, which may help us identify early changes and prevent cancer from developing.
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