Source: *The Straits Times*, pA16
Date: 1 May 2023

New study shows for the first time how cancer evades the immune system

Repeated exposure to disease exhausts cancer-killing cells but it is possible to reactivate them

Lee Li Ying

A research team led by the National Cancer Centre Singapore has discovered how cancer cells escape detection and destruction by the immune system – a feature that was previously unknown.

The findings have implications for the development of novel strategies for cancer treatment, bringing medicine closer to curing even the most lethal of cancers, researchers say.

The team, comprising members from Duke-NUS Medical School, KK Women's and Children's Hospital, the Agency for Science, Technology and Research's (A*Star) Singapore Immunology Network, the University of Southampton and the Alan Turing Institute, had their breakthrough discovery published in scientific journal Nature Communications on March 27.

Professor Gopal Iyer, senior author of the study and head of the Department of Head and Neck Surgery, Division of Surgery and Surgical Oncology, Singapore General Hospital and National Cancer Centre Singapore, said the immune system searches for and destroys abnormal cells such as cancer cells.

But in some instances, cancer cells avoid being detected and killed by the immune system and are able to develop and spread more easily, he added. Metastasis, a process when cancer cells break away from the primary tumour and form in other parts of the body, makes cancer harder to treat and results in poorer prognosis.

Professor Gopal Iyer says there are multiple pathways to effectively treat cancer – by targeting cancer cells, the immune system and using existing therapies to counter immune-system evasion by cancer cells. PHOTO: NATIONAL CANCER CENTRE SINGAPORE

For this reason, the team decided to investigate early onset of metastasis, which typically occurs when cancer cells are detected in lymph nodes near the primary tumour. They profiled primary and metastatic lymph-node tumours from 14 patients with head and neck squamous cell cancers.

The team found pre-metastatic cells within the primary tumours with the capacity to metastasise to the lymph nodes. They also found that a substantial proportion of CD8+ cells, a key component of the immune system that searches for and kills abnormal cells such as cancer cells, were "exhausted" and unable to perform their protective role. This occurred when the immune cells were repeatedly exposed to cancer and unable to eliminate it.

"Like an unethical employer that forces their employees to work continuously, cancer forces the immune cells to work overtime and become exhausted, rendering them incapable of functioning normally," said Prof Iyer.

The researchers also discovered a new pathway – called Midkine receptors – that allows the cancer cells and CD8+ immune cells to talk to each other.

Prof Iyer said that when the Midkine pathway is activated between the cancer cells and the immune cells, the cancer cells are effectively emitting a "don't eat me" signal.

"If you block this pathway and treat it with anti-PD1 treatment (an anti-cancer drug), you convert this 'don't eat me' signal to an 'eat me' signal and reactivate the killer CD8+ cells," he added.

But some cancer cells continued to show their ability to escape immune surveillance.

"Just like some employees who are too burnt out to work properly even with a bonus, some immune cells were seen to remain exhausted even after treatment, which is how cancer may not be detected and effectively destroyed by the immune system," said Prof Iyer.

Despite that, one key takeaway from the findings is that the ability to activate the immune system still works even after the cancer has spread.

He added that in normal cancer treatment, CD8+ immune cells in the tumour and lymph nodes are usually destroyed. The findings of the study indicate that more care is needed when targeting such cells, because they can be reactivated to target the cancer cells later.

"Our investigations indicate that we can use multiple pathways to effectively treat cancer – by targeting cancer cells, the immune system and using existing therapies to counter immune-system evasion by cancer cells.

"We know we need an increased arsenal of weapons to use against cancer and have to put it together to improve treatment outcomes," said Prof Iyer.

liyinglee@sph.com.sg