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Researchers discover how a virus transforms immune cells into cancer

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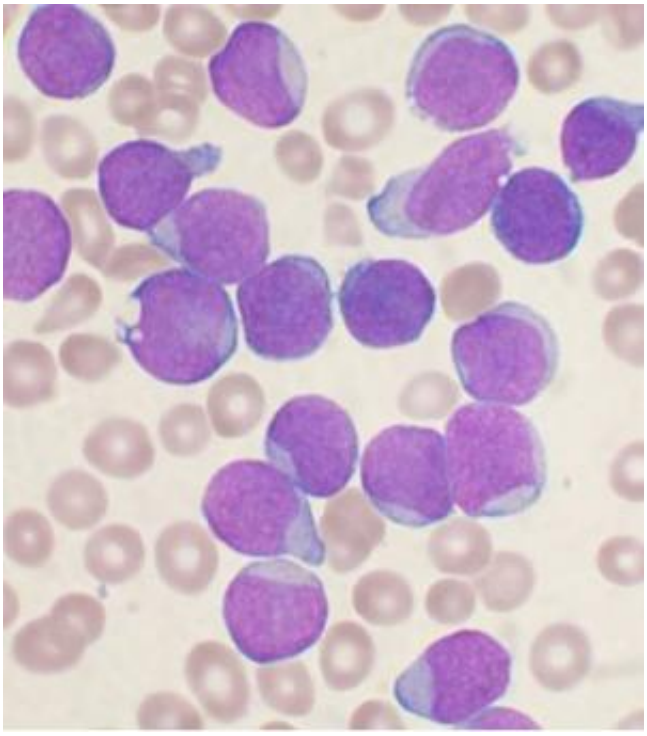

A Wright's stained bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

An international team have mapped how the HTLV-1 virus causes a rare leukemia in some people, providing clues on how to stop it happening.

The team, led by Imperial College London and Kumamoto University in Japan, used single-cell analysis to show how the virus over-activates T-

cells, key immune cells in our blood, causing them to turn cancerous.

The rare cancer, called adult T-cell leukemia/lymphoma (ATL), develops in around five percent of people infected with the HTLV-1 virus, but only several decades after initial infection. HTLV-1 infects T-cells specifically and transforms them into leukemia cells, but the time lag has made it extremely difficult to determine how this transformation occurs.

ATL can progress slowly or aggressively, but there is no standard treatment for high-grade ATL, and the condition has a high relapse rate after treatment with chemotherapy and antiviral drugs.

The team's results, published today in the *Journal of Clinical Investigation*, reveal that the virus hijacks the activation machinery of T-cells, causing them to persist at a high level of activation, gradually becoming malignant.

Co-lead researcher Professor Yorifumi Satou, from Kumamoto University is a virologist studying HTLV-1. He said: "While only a small percentage of people with HTLV-1 viral infections go on to develop adult T-cell leukemia/lymphoma, there are estimated to be around five to ten million carriers of the virus worldwide, and in some areas it is endemic—for example there are around one million cases in Japan."

Co-lead researcher Dr. Masahiro Ono, from the Department of Life Sciences at Imperial, is an immunologist and cell biologist who brought his knowledge of T-cells to the project. He said: "There is therefore a great need to understand how the virus turns our T-cells against us in the progression to cancer. Our work highlights a key mechanism for this change and provides us with new directions to search for ways to interfere with the process, potentially preventing the cancer from developing."

Leukaemias are cancers originating from blood or bone marrow cells, characterized by large increases in the number of abnormal white blood cells. T-cells are special kinds of white blood cells that are crucial for fighting off invaders, such as viruses and bacteria.

The HTLV-1 virus inserts itself into one type of T-cell, and, to begin with, remains there in a 'latent' state, not releasing any new virus particles or causing any ill effects. For many such carriers of the virus, this never changes, but in around five percent of carriers, after decades of latency the virus reawakens and affects the T-cells' functioning.

The team studied more than 87,000 T-cells from virus-free donors, healthy carriers of the virus, and patients with ATL. They sequenced the RNA (a simpler form of DNA) from these cells to find out how the virus and the T-cells were interacting.

They revealed that, in people who progressed to ATL, HTLV-1 made infected T-cells highly activated and over-reactive, causing them to over-produce proteins that keep them proliferating and helping them avoid other parts of the immune system that would usually remove rogue cells.

The team thinks that these changes made the overactive T-cells more vulnerable to DNA damage, such as through chemical agents or radiation, accelerating their transition to a cancerous state.

Further study of the processes involved, say the authors, will lay the foundations for potential new treatment options. Dr. Ono said: "For example, the chronic activation of T-cells could be halted by molecules that block signaling pathways that tell the cells to activate. Alternatively, treatments could target the proteins the activated T-cells create to help them proliferate."

More information: Benjy J.Y. Tan et al, HTLV-1 infection promotes

excessive T cell activation and transformation into adult T cell leukemia/lymphoma, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI150472