Mutations in gene SETD2 make cancer cells vulnerable to drug inhibiting the protein WEE1

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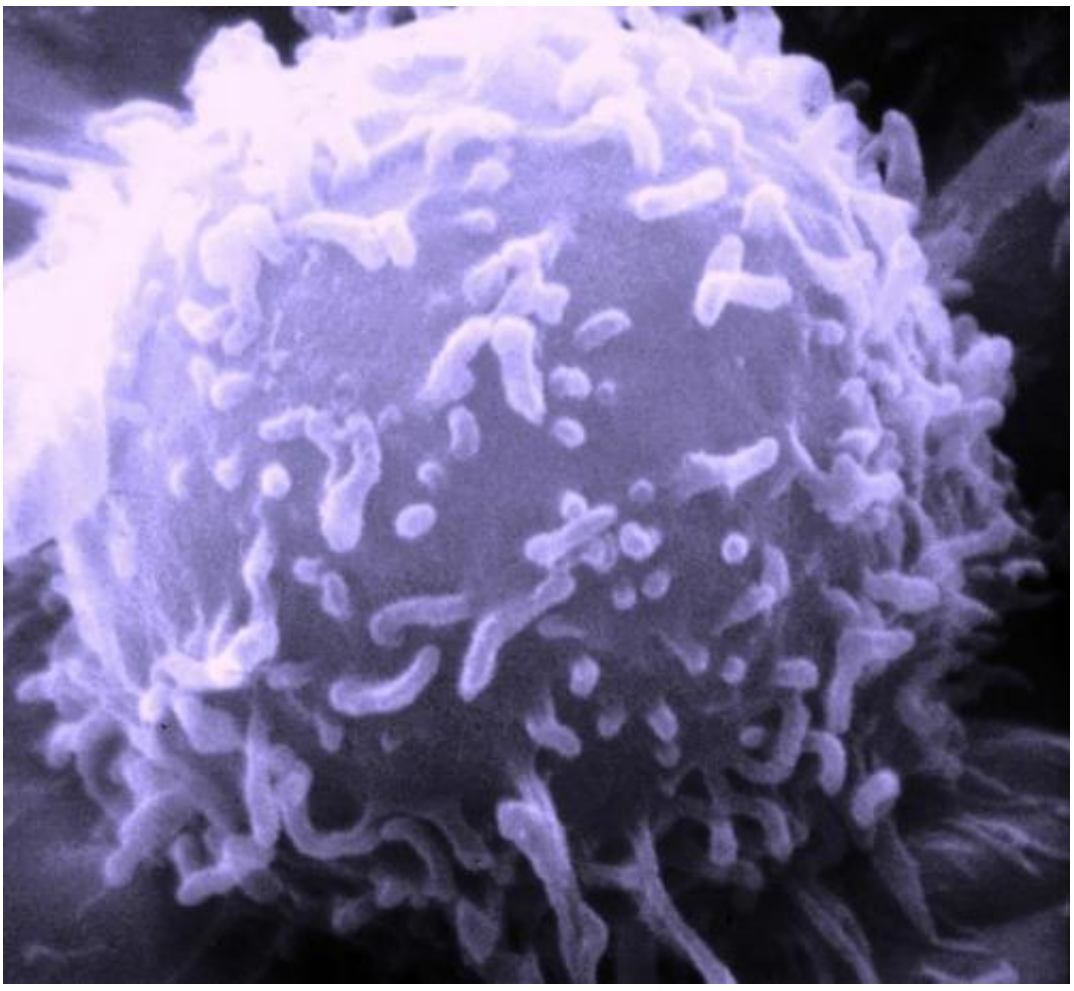

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Oxford University researchers have found the Achilles heel of certain cancer cells - mutations in a gene called SETD2. Their findings will be presented to the National Cancer Research Institute conference in Liverpool this Monday.

It is well known that mutations drive cancer cell growth and resistance to treatment. However, these mutations can also become a weak point for a tumour. The Oxford team found that that was the case for cancer cells with mutations in a key cancer gene called SETD2.

Study author, Dr Timothy Humphrey said "Mutations in SETD2 are frequently found in kidney cancer and some childhood brain tumours, so we were excited when we discovered that a new drug we were studying specifically killed cancer cells with this mutation."

The presentation will discuss how Dr Humphrey and his team showed that cancer cells with a mutated SETD2 gene were killed by a drug called AZD1775 that inhibits a protein called WEE1. WEE1 was first discovered by British Nobel Prize winner Sir Paul Nurse.

The team achieved this by exploiting the concept of 'synthetic lethality", where a combination of two factors kills a cancer cell. This has the potential to be a less toxic and more effective treatment than more standard approaches because it can specifically target cancer cells.

Co-author Dr Andy Ryan said: "When WEE1 was inhibited in cells with a SETD2 mutation, the levels of deoxynucleotides, the components that make DNA, dropped below the critical level needed for replication. Starved of these building blocks, the cells die. Importantly, normal cells in the body do not have SETD2 mutations, so these effects of WEE1 inhibition are potentially very selective to cancer cells."

Importantly, the research team, funded by Cancer Research UK and the

Medical Research Council, have also developed a biomarker test to identify SETD2 mutated tumours, something that can be used immediately in cancer diagnosis.

Professor Tim Maughan, Clinical Director of the Cancer Research UK/ Medical Research Council Oxford Institute for Radiation Oncology, said "This novel and exciting finding provides a new scientific basis for precision targeting of some cancers which are currently very difficult to treat, and we are now taking these findings into clinical trials."

While there is still work to do before a treatment is available, the hope is that these findings will help to target other cancers with similar weak points and provide a step towards personalized cancer therapy.

More information: SophiaX. Pfister et al. Inhibiting WEE1 Selectively Kills Histone H3K36me3-Deficient Cancers by dNTP Starvation, *Cancer Cell* (2015). DOI: 10.1016/j.ccell.2015.09.015

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