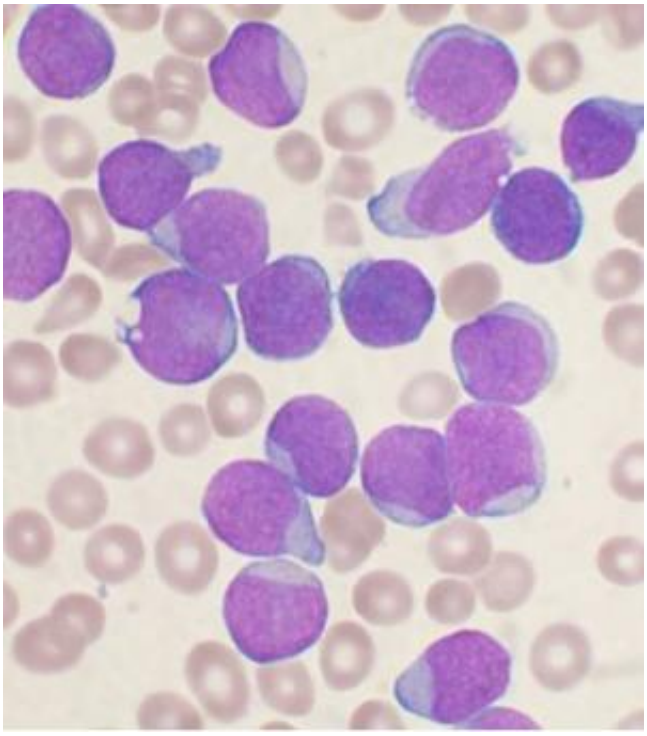
Metabolism drives growth and division of cancer cells

February 20 2017



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

The metabolic state of tumor cells contributes to signals that control their proliferation. German biochemist and Nobel Prize laureate Otto H. Warburg observed in the 1920s that tumor cells radically change their metabolism. This process was termed "Warburg Effect," but was neglected until recently by cancer research. The latest results show it is,

indeed, of fundamental importance for the development of aggressive tumors. Richard Moriggl and his co-workers have now published in the journal *Leukemia* how the tumor promoter STAT5 integrates metabolic signals that contribute to oncogenic transformation. Researchers from the VetmeduniVienna, Ludwig Boltzmann Institute for Cancer Research and Meduni Wien may have thus identified a new target to tackle cancer.

STAT5 controls maturation and division of blood cells. During the development of blood cells, it is activated by tyrosine phosphorylation and can switch certain genes on or off. This activation is transient in healthy cells, but STAT5-dependent tumor cells produce a continuous signal resulting in long-term phosphorylation. This changes, among other things, the pattern of genes controlled by STAT5 and the cells begin to divide uncontrollably resulting in a STAT5-dependent leukemia.

Metabolism changed in cancer cells

To live, every cell needs not only energy, but also building materials. Complex metabolic processes provide cells with the necessary building blocks to grow and then divide. In a healthy cell, an equilibrium of metabolic processes is established, in which most sugar is completely "burned" into carbon dioxide for energy production. In cancer cells, this balance is shifted. Sugar is no longer completely oxidized for energy production, but intermediates are increasingly used for growth and rapid cell division.

Leukemia factor STAT5 is sugar-dependent

The sugar molecule UDP-GlcNAc serves as an indicator for the energy supply of the cell. If the cell is well supplied with nutrients, this molecule is abundant and signals to the cell that the tank is full. A specific enzyme (OGT) can attach this sugar molecule to a variety of proteins as a

marker, thus controlling metabolic processes. "We are investigating STAT5, which can be marked with GlcNAc at a specific site (T92). By means of genetic engineering, we have produced a variant of STAT5, which cannot carry this chemical group to decipher its influence on this oncogene. This variant is, so to speak, blind to the indicator and simulates the state of an empty tank," explains the first author Patricia Freund from the Institute for Animal Breeding and Genetics of Vetmeduni Vienna.

Findings may lead to new therapy

The researchers have now discovered that the STAT5 variant is not persistently tyrosine-phosphorylated without GlcNAc labeling. Thus, the sustained activation necessary for the transformation of cells into cancer cells is lacking. "If the tank is empty, the cell cannot divide," explains Moriggl. The signals of a good supply of nutrients, ie a high concentration of UDP-GlcNAc, are a precondition that oncogenic signals reach the cell nucleus via STAT5. "So we can turn off STAT5 if we trick it into believing the cell's nutrient supply is exhausted. Together with our collaboration partners, we will now perform experiments to explore whether this principle might have therapeutic potential," says Moriggl regarding the translational aspects of his research.

More information: P Freund et al. O-GlcNAcylation of STAT5 controls tyrosine phosphorylation and oncogenic transcription in STAT5-dependent malignancies, *Leukemia* (2017). DOI: 10.1038/leu.2017.4

Provided by University of Veterinary Medicine—Vienna