Ludwig Boltzmann Institute
Cancer Research

**EMBARGO: 6:00 CET, February 20,2017**

# Metabolism drives growth and division of cancer cells

***The metabolic state of tumor cells contributes to signals that control the proliferation of tumor cells. Already the 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", however neglected until recently by cancer research, but 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 Ludwig Boltzmann Institute for Cancer Research, Vetmeduni 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 in healthy cells transient, 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.

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.

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 at the University of Veterinary Medicine Vienna.

The researchers have now discovered that the STAT5 variant is not persistently tyrosine-phosphorylated without GlcNAc labeling. Thus, the sustained activation which is necessary for a 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. We together with our collaboration partners will now perform experiments to explore whether this principle might have therapeutic potential," emphasizes Moriggl the translational aspects of his research.

This research was carried out with financial support by the private Melanoma Donation in Liechtenstein and was partly funded by the FWF through SFB-F28 „Jak-Stat Signalling: from Basics to Disease“ and SFB-F47 "Myeloid Neoplasia".

## Service:

P Freund, M A Kerenyi, M Hager, T Wagner, B Wingelhofer, H T T Pham, M Elabd , X Han , P Valent, F Gouilleux, V Sexl, O H Krämer, B Groner and R Moriggl: ***O-GlcNAcylation of STAT5 controls tyrosine phosphorylation and oncogenic transcription in STAT5-dependent malignancies*** Leukemia accepted article preview 11 January 2017; doi: 10.1038/leu.2017.4

http://www.nature.com/leu/journal/vaop/naam/abs/leu20174a.html

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## About the Ludwig Boltzmann Institut for Cancer Research (LBI-CR):

The LBI-CR focuses on developing new murine models for cancer and exploiting them to gain novel insights into the origins of the disease. The institute conducts cutting edge research into the underlying mechanisms of cancer using the modern power of genetics. With particular attention for signal cooperation in tumour cells the researchers analyse the molecular basis of cancer with the intention to translate recent progress in cancer research into novel therapeutic approaches. The Institute conducts its research in close cooperation with the Research Institute for Molecular Pathology, Medical University Vienna, University of Veterinary Medicine Vienna, Children's Cancer Research Institute and the company TissueGnostics.

## About the Ludwig Boltzmann Gesellschaft:

The Ludwig Boltzmann Gesellschaft (LBG) is a non-university research organization headquartered in Vienna. It operates research institutes (Ludwig Boltzmann Institutes) in the fields of human medicine / life sciences, as well as the humanities, social and cultural sciences. It initiates innovative research topics together with academic partners and stake holder organisations, including companies, associations and ministries. The LBG is specialized in translational research - the bridge between basic research and application. In the humanities and social sciences institutes, the interdisciplinary research results are communicated to the specialist audience at conferences and scientific events, as well as made accessible to the general public through public activities.

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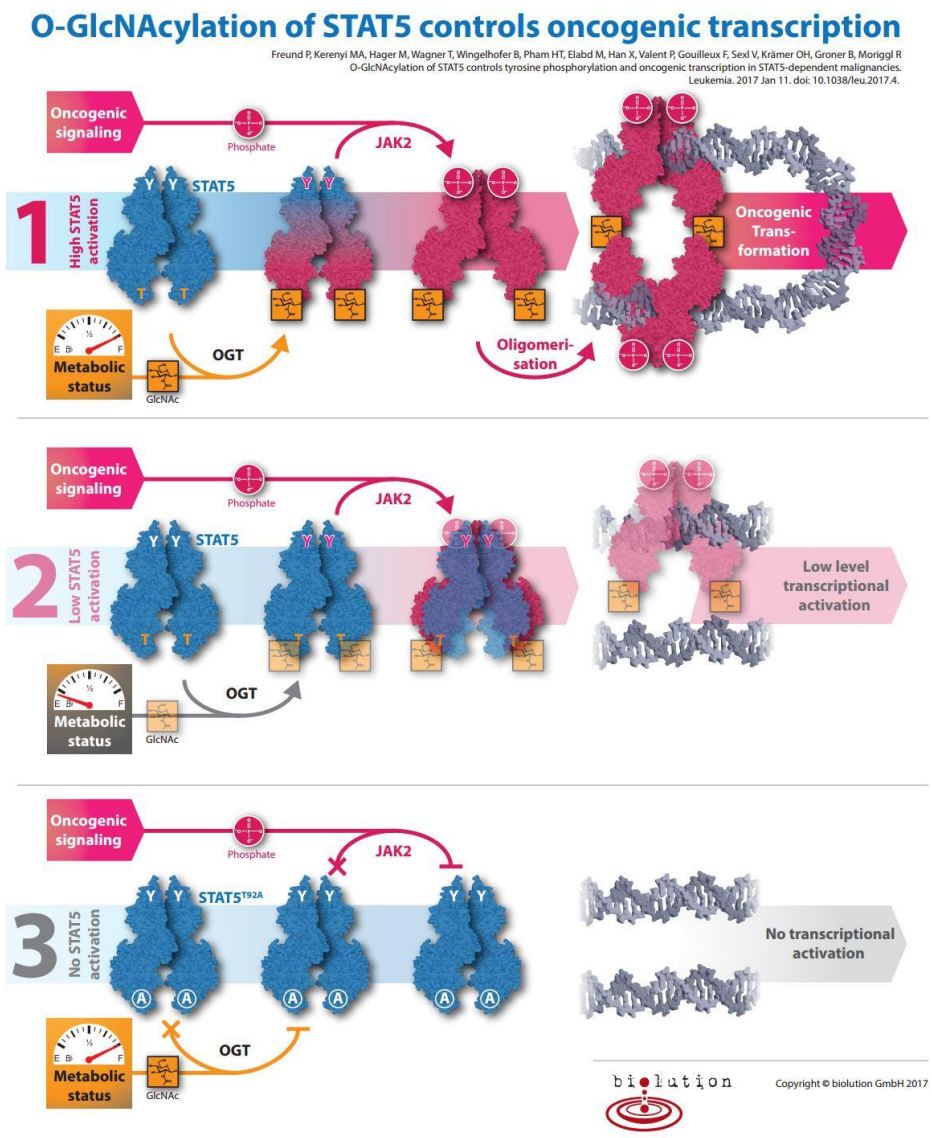
## Graphical Abstract:




The metabolic status of the cell and its supply of nutrients is signaled, amongst other, by the O-linked N-acetylglucosamine (GlcNAc) transferase (OGT). This enzyme links GlcNAc (**orange squares**) as a mark to STAT5 at the OH groups of threonine 92 (T). Cytokine receptors activate the kinase JAK2, which phosphorylates STAT5 on tyrosine 694 (Y) (**red circles**). If a cell receives oncogenic signals via JAK2 and is well supplied with metabolites **(1)**, much STAT5 is labeled with GlcNAc on T92 (T) and JAK2 can phosphorylate STAT5 efficiently on Y694 (Y). A high concentration of STAT5 is translocated in the nucleus, binds to available promoters and might oligomerize to influence the genomic landscape by looping DNA.

If the cell is not adequately supplied with nutrients **(2)**, even strong oncogenic activation of JAK2 leads only to a moderate increase of active STAT5 carrying a GlcNAc at T92 (T) and a phosphate at Y694 (Y). Thus, only a few STAT5 proteins are present in the nucleus, binding to DNA to activate target genes. Oligomerisation is not detectable.

If STAT5-T92 is replaced by site directed mutagenesis **(3)** with an alanine (A), OGT can no longer transfer GlcNAc onto this position regardless of the metabolic status of the cell. STAT5 has effectively become blind to the nutrient supply and JAK2 fails to activate it. The oncogenic signal is effectively attenuated, thus OGT is a potential target for pharmacological development.