Scientists shed new light on mechanisms of T-ALL, a form of leukemia that primarily affects children

23 December 2012

Acute lymphatic leukemia (ALL) is the most common cancer in children under the age of 14 years. With optimum treatment, approximately 75 % of children are currently cured, but the treatment consists of severe chemotherapy with many side effects. In collaboration with international research teams, scientists at VIB, KU Leuven and UZ Leuven have identified new genetic mutations that lead to T-ALL, a variant of ALL. They have unmasked the ribosome – the molecular machine in the cell that is involved in the production of proteins – as a weak spot in leukemia cells. Their research has also shown that there is a difference in T-ALL between adults and children. Both findings can be important in the search for improved treatments for T-ALL.

Jan Cools (VIB/KU Leuven):"We have discovered that there is a clear genetic difference between T-ALL in children and in adults. This could be an explanation why adults do not respond as well to the current therapy."

Stein Aerts (KU Leuven):"This is a beautiful example of the power of genome sequencing in cancer research. New technologies and large-scale bio-informatics allow us to study a lot of data simultaneously. This allows us to discover links that would have been impossible to find in the past."

T-cell acute lymphatic leukemia (T-ALL)

The formation of white blood cells is disrupted by leukemia. The cells in the bone marrow that should mature into white blood cells multiply unchecked without maturing completely. These immature blood cells compromise the production of normal blood cells. This makes patients more susceptible to infections. Leukemia occurs in different forms; in the case of T-ALL, there is an accumulation of immature white blood cells over a very short period of time. With optimum treatment – involving chemotherapy – approximately 75 % of children are currently cured. For adults, the chance of a cure is below 50 %. Chemotherapy is associated with many side effects. The search for a more specific treatment can only start once we know what causes T-ALL.

7 new genes with a key role in T-ALL identified

T-ALL only occurs if errors in various genes occur simultaneously. It is important to determine which genes play a key role. Kim De Keersmaecker, Zeynep Kalender Atak, Jan Cools and Stein Aerts have identified a series of defects in 15 important genes, of which 7 have not previously been associated with T-ALL. They used next-generation sequencing to analyze the 20,000+ genes of 67 T-ALL patients. This technique allows for very fast analysis and comparison of the complete DNA sequence of healthy and sick individuals.

A difference between adults and children

The investigators from Leuven also discovered a difference between T-ALL in children and in adults. T-ALL in adults contains significantly more mutations than in children. The leukemia cells in adults also contain mutations in other genes than in children. This genetic difference could be a possible explanation why adults do not respond as well to the current therapy.

A weak point in leukemia cells exposRPL5 and RPL10 – two newly identified genes – form A weak point in leukemia cells exposed

RPL5 and RPL10 – two newly identified genes – form part of the ribosome: this is the complex in the cell that produces proteins. The scientists hereby

demonstrated for the first time that defects in the ribosome can also play a role in cancer activation. Experiments in yeast cells confirm that mutations in RPL10 cause a change in the ribosome.

Kim De Keersmaecker (VIB/KU Leuven):"This could be a weak point of the leukemia cells: all cells need properly functioning ribosomes to survive and to grow. These 'defective' ribosomes in the leukemia cells could be a new suitable target for the development of targeted therapies."

More information: Exome sequencing identifies mutation of the ribosome in T-cell acute lymphoblastic leukemia. Kim De Keersmaecker et al. *Nature* 2012.

Provided by VIB (the Flanders Institute for Biotechnology)