MedicalXpress

Scientists find new mutations in leukemia

September 4 2011

An international team of researchers has found a group of mutations involved in T-cell acute lymphoblastic leukemia (T-ALL), and showed that certain drugs, already in clinical use to treat other diseases, can eliminate the cells carrying these mutations.

Results will be published next week in Nature Genetics and may promote the development of novel therapeutic approaches against leukemia.

The study was led by researcher Joao T. Barata at Instituto de Medicina Molecular in Lisbon, Portugal, jointly with J. Andres Yunes at Centro Infantil Boldrini in Campinas, São Paulo, Brazil, in collaboration with researchers from the National Cancer Institute in Frederick, Maryland, USA, the Erasmus Medical Center, Rotterdam, The Netherlands; and other laboratories in Europe and the US.

This is a basic research study with potential clinical impact, which was performed, in part, using samples from pediatric leukemia patients.

T-ALL affects mostly children. It is a blood cancer consisting in an uncontrolled growth in the number of T-lymphocytes (white blood cells from the immune system).

The onset of the disease can be triggered by different genetic mutations in genes involved in the proliferation and differentiation of T-cells.

The identification and study of mutations found in leukemia patients is

particularly important to help develop more efficient and targeted therapies. Researchers now found a group of mutations that affect 9% of the patients with T-ALL and that may originate leukemia in these patients.

Most importantly, researchers demonstrated that a set of pharmaceutical drugs can eliminate the effect of these mutations, unraveling a potential therapeutic application for their discovery.

The current study shows that the mutations occur at the gene coding for a protein localized at the surface of T-cells, the interleukin-7 receptor (IL7R).

This protein contacts with both the exterior and the interior of the cells, acting as a bridge to transfer chemical information from the outside to the inside of cells. Information transfer occurs upon the binding of a bloodstream protein (interleukin-7) to the receptor, which triggers a cascade of cellular reactions that are essential for the correct development and proliferation of T-cells.

In the new study, researchers also found that the mutations promote non-stop, uncontrolled T-cell proliferation, independently of extracellular triggers. This capacity to induce cells to grow relentlessly is associated with the ability to originate tumors.

To help fighting the tumors that contain IL7R mutations, the team of researchers studied pharmaceutical drugs known to act in several steps of the referred cascade of cellular reactions and found that these drugs - which are already being tested against other diseases such as rheumatoid arthritis – can stop cell proliferation induced in mutated cells and promote the elimination of these cells.

Says João T. Barata: "We discovered that the interleukin-7 receptor,

which is essential for proper T-cell development, may also have a "dark side", acting as a Mr. Hyde of sorts. In particular, we found that certain mutations in this gene are involved in pediatric T-cell acute lymphoblastic leukemia and characterized how they act. Our observations allowed us to identify potential therapeutic weapons against these tumors. Although pediatric acute lymphoblastic leukemia is among the success stories in cancer therapy, improvements are still needed. We hope our findings will help further increase the efficacy and selectivity of already existing treatments."

Says J. Andrés Yunes, from Centro Infantil Boldrini in Campinas, São Paulo, Brazil: "Most mutations found resulted in the insertion of a cystein aminoacid into the IL7R. It is this new cystein that perverts the normal functioning of the receptor by linking two mutant IL7R molecules through disulfide bonds. I'm eager to know what is the probability of having a cystein codon insertion, in this specific location of the gene, to address whether this is random or not."

Says Scott K. Durum, from the National Cancer Institute in Frederick, Maryland, USA: "On the one hand, the IL-7 receptor should have seemed a likely cause of cancer because it normally stimulates cells to grow, which is what cancer cells do. On the other hand this seemed unlikely because there are normally two chains involved in signaling. However these remarkable mutations in just one of the chains circumvent the need for the second chain. In addition to existing drugs that can target this pathway, we aim to develop new antibodies against IL-7 receptor to treat these patients. "

More information: "Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia", Priscila P. Zenatti, et al. *Nature Genetics*.

Provided by Instituto de Medicina Molecular