

Molecular Pathways in T-Cell Acute Lymphoblastic Leukemia: Ramifications for Therapy

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What is the current outlook for patients with T-cell acute lymphoblastic leukemia?

Acute lymphoblastic leukemia (ALL) is more common in children than in adults. T-cell ALL (T-ALL) can occur at any age, but it most commonly presents in the teenage years, and the incidence levels off in adulthood. It is a leukemia of thymic T-cell progenitors before they become effector T cells. The outlook is somewhat better in children than in adults, although it is uncertain why. Some of the best treatment programs, such as that developed by Dr. Stephen Sallan and his colleagues at Dana-Farber Cancer Institute, has a cure rate of 75% or better in children and young adults with T-ALL.

How is the outlook different for adults with this disease?

In adults with T-ALL, the outcome has not been as good. We are now testing in young adults, under the age of 45, some of the very intensive treatments that have been pioneered in children. However, patients over age 45 cannot tolerate chemotherapy at the level of intensity used to achieve outstanding results in children. In any case, a great deal of attention is focused on improving outlooks in high-risk patients, both children and adults, who are failing current treatment, and developing targeted treatments that are less toxic to normal cells. All of the current regimens for T-ALL are very intensive, and so it is especially desirable to have more specific treatments for this disease.

Is the search for molecular pathways in T-ALL only beginning, or is it already fruitful?

The search for molecular pathways in T-ALL is quite a fruitful area of research, and it actually began at least 15 years ago with the discovery of genes involving chromosomal translocations in T-cell leukemia and T-cell lymphoma. The principle is that the T-cell receptor loci are expressed at high levels due to potent enhancers that are activated in thymocytes. The translocations often place oncogenic transcription factors adjacent to these promoter elements and drive inappropriate levels of expression of these master regulators of development. This can happen at a stage of

T-cell development when the process contributes to one or more aspects of malignant growth and aberrant survival of the cells.

About 5 years ago, Dr. Adolfo Ferrando and colleagues at Harvard Medical School studied expression of these genes and found larger numbers of cases that overexpressed these critical oncogenes for other reasons. We now believe that there are about 5 major pathways that can lead to T-ALL, each of which involves the overexpression of 1 or more oncogenic transcription factors and the loss of tumor suppressor genes. Recently we have learned that this process also involves mutational activation of the NOTCH1 receptor; NOTCH1 is a gene encoding a transmembrane receptor that regulates normal T-cell development.

The emerging picture is of 5 multistep pathways that can lead to T-ALL in humans. These pathways seem to be the same in children and adults, but there is a difference in the prevalence of each of these pathways in younger compared with older patients.

Are these 5 pathways present in all patients?

These are 5 pathways that we used to believe were completely distinct; the recent discovery of the NOTCH mutation now links them to an extent. It is difficult to determine the order in which mutations occur in this disease, but we now think a likely scenario might be that the NOTCH receptor mutations occur first because they drive T-cell commitment and proliferation. From there, the pathways diverge, and different types of oncogenes and tumor suppressors combine together synergistically to cause leukemia.

Does the ability to identify these pathways help to identify different subtypes of T-ALL?

Disease caused by any of these pathways is clinically indistinguishable. They can only be distinguished at the molecular level. However, different receptor mutations do indicate different prognoses. One pathway involves a homeotic transcription factor called OX11, and this group seems to be very responsive to chemotherapy and to have an excellent outcome with currently available chemotherapy. Some of

the other molecular subgroups are higher risk, with a higher chance of treatment failure.

Will targeting a molecular pathway eventually lead to a cure?

Cure is the goal of current work. It will take at least a decade to bring current research to better targeted treatments that are curative. One problem with this approach is that the transcription factors that have been identified as being overexpressed and contributing to T-cell leukemia are not good targets for the kind of small-molecule drugs that are currently available. Therefore, a problem we now face is to find molecules that are better drug targets and that are parts of these pathways. It is believed that these most likely will come from gene expression microarray studies that are now ongoing.

How is the development of drugs that target T-ALL molecular pathways being approached?

A logical approach would be to develop a drug that specifically targets the oncoprotein that we know is overexpressed and contributes to T-cell leukemia. This has not proved generally feasible because transcription factors in the nucleus that regulate gene expression are difficult to target with small-molecule drugs. Most small-molecule drugs target receptors, enzymes, or channel proteins, for example, but not transcription factors.

The discovery of the NOTCH1 mutation, reported in *Science* by our group and Dr. John Astor's lab at Brigham and Women's Hospital in Boston, has very definite, direct clinical implications. Our research implicated the NOTCH pathway in a high percentage of cases of T-ALL: at least 60%, and this number may be quite a bit higher when we have identified all of the possible mutations. NOTCH1 is a cell surface receptor. There are several different ways it could be targeted, including antibodies and drugs that inhibit enzymes involved in the processing of the receptor, such as metalloprotease inhibitors and gamma secretase inhibitors. Therefore, this new discovery has opened up much more direct avenues to targeted treatment, which we are actively pursuing.

Will entirely new ways of targeting the NOTCH1 pathway have to be developed?

It was fortuitous to discover that the same gamma secretase enzyme complex that cleaves the NOTCH receptor is also involved in degrading the amyloid proteins that contribute to cell death in Alzheimer disease. A number of companies have developed inhibitors of this enzyme, which may now have application in T-cell leukemia.

Will the discovery of the NOTCH receptor change the direction of future research?

This work on the NOTCH receptor will definitely influence research. In order to develop effective targeted treatment for this disease, we need a molecule that the leukemia cells require for their survival and growth and which differentiate them from normal cells. Until now, the obvious targets were not good drug targets, but the NOTCH pathway looks very promising. We have to wait for results from clinical trials to understand how effective this will be.

Is the NOTCH pathway specific to T-ALL, or will it have implications for other types of ALL?

As far as we know, the NOTCH pathway is quite specific for T-ALL. It is too early to be certain, and there is definite interest in finding whether other cancers will be responsive.

Are there other pathways beyond the NOTCH pathway that will be useful in treating T-ALL?

The NOTCH pathway presents several other logical means of interfering with leukemia development. For example, we were recently involved in a discovery that a subset of T-cell leukemias express an activated abl kinase that is similar to but distinct from the abl kinase that causes chronic myelogenous leukemia, and so we believe patients with this type of leukemia will respond to imatinib (Gleevec, Novartis). The approach may only be effective in 5–10% of patients, but this discovery opens up another avenue for clinical trials

The trend in the future will be detailed analysis of the molecular abnormalities in each patient's cells and, based on this, therapies tailored to the molecular pathways that are activated in the patient's leukemia.

At present, does the identification of certain targets in a patient effect how he or she is treated?

We published a paper in the *Lancet* in which we reported that the OX11 group, which comprises only about 5% of children but as many as 30% of adults with T-ALL, is a group that will respond very favorably to currently available chemotherapy. For this group, we advocated a regimen of very high-dose chemotherapy with stem-cell rescue.

Risk stratification is an important area of research now. We have been able to identify 30% of adults who we think will have very good prospect of cure with standard chemotherapy, but a goal is to identify high-risk patients at diagnosis. It is realistic to be working toward a cure for every patient who presents with this disease, and it is known that the best chance for cure is immediately at diagnosis.

Are there any new drugs that are anticipated to show promise in treating T-ALL?

We now have several attractive targets for T-ALL, and we are looking forward to testing drugs that target these pathways. Some are preclinical and some are very close regulatory approval. We are hoping for more drugs along the lines of imatinib because its high level of activity and low toxicity for chronic myelogenous leukemia have changed the whole outlook for that disease.

Suggested reading

Weng AP, Ferrando AA, Lee W, et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science*. 2004;306:269-271.

Ferrando AA, Neuberg DS, Dodge RK, et al. Prognostic importance of TLX1 (HOX11) oncogene expression in adults with T-cell acute lymphoblastic leukaemia. *Lancet*. 2004;363:535-536.

Ferrando AA, Look AT. Gene expression profiling in T-cell acute lymphoblastic leukemia. *Semin Hematol*. 2003;40:274-280.