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Mutations in JAK3 gene identified in subtype of lymphoma provide potential drug target

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A substantial proportion of NK/T-cell lymphomas harbor Janus Kinase 3 gene mutations. Patients with these lymphomas might benefit from treatment with a Janus Kinase inhibitor according to a study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Very little was known about the genetic and molecular defects causing NK/T-cell lymphoma before we started this work," said Bin Tean Teh, M.D., Ph.D., director of the National Cancer Center Singapore-Van Andel Research Institute Translational Research Laboratory at the NCCS, and professor at the Duke-NUS Graduate Medical School in Singapore. "There is no effective treatment and this type of cancer carries an extremely poor prognosis.

"It is tremendously rewarding to have identified genetic mutations that appear to have an important role in driving the cancer in a considerable fraction of cases. Moreover, we are excited that there is a drug already in phase III trials for the treatment of rheumatoid arthritis that targets the mutant protein. We are in the process of planning a clinical trial to study whether this drug benefits NK/T-cell lymphoma patients," said Teh.

NK/T-cell lymphoma is a very aggressive form of lymphoma. It is particularly prevalent in Asia.

"Many years ago, I and a colleague came to the Van Andel Research Institute in Grand Rapids, Mich.," said Teh. "My colleague unfortunately

developed NK/T-cell lymphoma and passed away. It was the only case of this cancer ever diagnosed in Grand Rapids. As this illustrates, it is a relatively rare subtype of lymphoma in the United States, but it is responsible for the deaths of a large number of people in Asia, in particular in China and Korea. It accounts for almost half of all T-cell lymphomas in some parts of Asia.

"The passing of my colleague, whom I was very close to, was the reason that I started studying NK/T-cell lymphoma. It has been a complicated puzzle, but I feel that we have pieced together enough that we will have an impact on a large number of patients with this disease."

To identify genetic mutations that might have a functional consequence, Teh and his colleagues sequenced all the genes in NK/T-cell lymphoma cells from four patients. In addition to mutations in genes known to be associated with cancer, they detected mutations in the Janus Kinase 3 (JAK3) gene in the cancer cells from half of the patients. The researchers conducted follow-up sequencing of NK/T-cell lymphoma cells from an additional 65 patients and identified JAK3 mutations in 23 of those patients.

The mutations enabled NK/T-cell lymphoma cell lines to grow in culture in the absence of the normally essential growth factor IL-2. This meant that the mutations caused dysregulated activation of JAK3, and suggested that JAK3 might be a good drug target.

Consistent with this idea, a JAK inhibitor that is currently being assessed in phase III clinical trials as a treatment for rheumatoid arthritis killed cultured NK/T-cell lymphoma cell lines by a process known as apoptosis.

"We are currently putting together a proposal to test JAK inhibitors as a treatment for NK/T-cell lymphoma with JAK3 mutations," said Teh. "I

am hopeful that we might have found a molecular target for the treatment of a least some patients with this otherwise fatal disease."

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