Discovery suggests possible treatment strategy for aggressive leukemias

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Researchers at Duke University Medical Center have identified a mechanism that could explain how patients move into the worst phase of chronic myelogenous leukemia (CML).

Their findings implicate a protein called Mushashi that prevents cells from maturing, creating a large population of immature cells, which is one of the hallmarks of CML.

This same molecular pathway may also be related to other aggressive leukemias, as well as solid tumors like glioblastoma (a severe form of brain cancer) and breast cancer.

With collaborators at other institutions, the Duke team looked at 120 human specimens from patients representing different phases of CML progression. They found that Musashi levels increased dramatically as the disease became more aggressive.

"We found high levels of Musashi in all of the human advanced phase CML samples we studied," said senior author Tannishtha Reya, Ph.D., an associate professor of pharmacology and cancer biology at Duke.

"The fact that this pattern was seen in all of the human cells, regardless of patients' gender or ethnicity, and in people on three continents, marked it as potentially a major signal that needed to be studied in as much depth as possible," Reya said.

The work appears in *Nature* online on July 18.

Because CML progression is marked by a block in cell maturation (called differentiation) and an increase in immature cells, the team wanted to learn whether this was driven by an aberrant reversal of the signals that regulate cell differentiation. They focused on Numb, a molecule that is known to control differentiation during normal development.

The team used mice to compare the chronic (less harmful) and blast-crisis (most harmful and severe) phases of CML. They found much lower levels of Numb in the blast-crisis phase mice.

"It is not always clear if a pathway that appears to be important in mouse models will be relevant in human disease," Reya said. "In this case, however, the data and patterns are so strong in human patient samples that pursuing these findings becomes critical."

This led them to explore the way that Numb was being repressed in advanced disease, and whether this repression contributes to the maintenance of blast-crisis phase. They focused on the RNA-binding protein Musashi, which had previously been shown to repress Numb in other systems.

The Musashi protein was named for a Samurai warrior who fought with two swords, because the loss of Musashi in fruit flies (where the gene was discovered) resulted in a developmental defect in which flies had double bristles, reminiscent of Musashi's swords.

Reya's team found that Musashi is particularly elevated in stem cells and needed for their growth, which could help explain why it is co-opted to promote the growth of immature cells in cancers as well. Musashi expression was 10 times higher in the more immature blast crisis CML

phase. It may be a target for future therapies because blocking Mushashi could block cancer growth, Reya said.

"Our current work shows that activating Numb, or blocking Musashi can inhibit blast-crisis CML," Reya said.

Reya explained that there are two basic approaches to fighting cancer cell growth. One is to trigger programmed cell death in cancer cells or to block their growth directly. The other method, which may work in cases where the cancer is composed of immature cells, is to force these cells to mature and differentiate.

"The resulting depletion of immature cells can deliver a heavy blow to the continued growth of the cancer, as is seen in this study," Reya said.

Since high levels of Musashi appear to be an early marker of advanced CML, this might be a tool to determine patient prognosis as well, Reya said.

She said reports of higher levels of Musashi in glioblastoma and lower levels of Numb in high-grade breast cancer raise the possibility that the Musashi-Numb pathway could also be involved in solid cancers.

Provided by Duke University Medical Center