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Researcher pieces together AML prognosis puzzle

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When patients suffering from Acute Myeloid Leukemia (AML) express high levels of the gene, MN1, an already aggressive leukemia is accelerated and shortens survival time. While that's a known fact, the mechanisms involved aren't well understood which is why a Wake Forest Baptist Medical Center researcher decided to take a closer look.

Timothy S. Pardee, M.D., Ph.D., an assistant professor of hematology and oncology at Wake Forest Baptist, said that previous studies of AML have shown that when patients express high levels of the MN1 gene, chemotherapy doesn't help as much and they die sooner from the disease.

"No one really knows why this is happening," Pardee said. "Because this disease is treated only with chemotherapy we hypothesized that high expression of this gene, would make the leukemia resistant to chemotherapy treatment."

AML is an aggressive malignancy of the bone marrow where the white blood cells that usually protect people from infections become cancerous, leading to bone marrow failure and death. This cancer is characterized by a high relapse rate and resistance to chemotherapy. In older patients the average survival for those with high MN1 expression is less than six months while for low expressers it is closer to nine months.

The research was published online in August in PLOS One.

To test the hypothesis, Pardee set out to make leukemia cells express the MN1 gene and looked at how they changed in response to chemotherapy. He did this by using a retrovirus to add the MN1 gene and force high levels of expression in a genetically-defined mouse model of AML. This resulted in the mice having a worse prognosis compared to the group of mice that didn't get the MN1 gene. In addition, he also took the same retrovirus and put it into two separate human cell lines acquired from AML patients.

"We looked to see if the cells in both models were resistant to chemotherapy. The answer is 'yes,' though the resistance in mouse cells was more evident," Pardee said.

Then Pardee compared mouse leukemia cells that expressed high levels of MN1 and those that didn't to investigate what occurs when the cells are hit with chemotherapy. "It turns out there is a key protein, p53, that tells the cancer cells when DNA damage is too much and that it's time to commit suicide," Pardee said. "But p53 was not being made to the same level in those cells that were making the MN1 gene and the ability to turn that DNA damaged signal into leukemia cell death was much lower in the cells that make MN1 protein."

Pardee said he looked at some other proteins involved in leukemia cell death and found that an additional protein called BIM – which promotes cell death – was also being shut down in the cells that made higher levels of MN1.

"We know it's happening, but we don't know how. Our ultimate goal is to figure out better ways to treat these patients that do so poorly," Pardee said. "We were able to make the leukemia cells a little bit more sensitive to chemotherapy when we treated them with a drug that increases p53 levels, suggesting it might be a strategy to look at for patients who have this high MN1 expression.

Provided by Wake Forest University Baptist Medical Center