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Study shows protein complex essential to creating healthy blood cells

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A group of proteins best known for helping to activate all mammalian genes has been found to play a particularly commanding role in the natural development of specialized stem cells into healthy blood cells, a process known as hematopoiesis.

Researchers at NYU Langone Medical Center and its Perlmutter Cancer Center say their findings, which resulted from experiments in mice and human cells, suggest that placing strict biological controls on a portion of the protein complex, known as Mediator Complex Subunit 12, or MED12 for short, could serve as a tool for stopping a variety of cancers. MED12 mutations, they note, have been linked to several kinds of leukemia, as well as cancers of the prostate, uterus, and connective tissue.

Researchers say their latest experiments, described in a report in the journal *Cell Stem Cell* online Aug. 25, are believed to be the first to fill in the details about how MED12 is vital to the growth of hematopoietic stem cells, or HSCs, in bone marrow, to keep blood cells healthy. Three other proteins known to be tied to the active part of the mediator complex were tested and found to not be essential to HSC development, confirming MED12's prominence, they say.

"Because MED12 appears to be so essential to hematopoiesis, our study points to it as a possible target for future anticancer therapies for both chronic and acute forms of leukemia," says senior study investigator and NYU Langone cancer biologist Iannis Aifantis, PhD. "Our study also

suggests that MED12 hyperactivation or loss of control is a possible explanation for what factors may trigger these cancers and other solid tumors."

Aifantis, a professor and chair of the Department of Pathology at NYU Langone and a member of its Perlmutter Cancer Center, says it is becoming clear that the mediator complex and other proteins involved in gene activation and regulation, including enhancer and promoter stretches of DNA, are "not just innocent bystanders in gene transcription, but active participants in cell differentiation programs like hematopoiesis, both when these programs functions normally and when they go awry."

In their latest experiments, researchers analyzed what happened to HSCs in mice engineered to specifically lack the MED12 protein, after injection of a special activating molecule into the adult mice's bone marrow. All MED12-deficient mice died within two weeks after injection, with shrunken spleen and thymus tissues considered evidence of insufficient and underdeveloped blood cells.

Subsequent analyses of the animals' bone marrow, where the stem cells reside, showed that estimates of early progenitor and other undifferentiated blood cells diminished in each mouse from nearly 150,000 to 15,000 within four days post injection. Deleting other protein factors showed much less dramatic depletions in blood cells and did not kill any mice, providing further evidence that MED12—by loss of its function alone—is essential for hematopoiesis, researchers say.

In another set of laboratory experiments using human HSCs, researchers found that deleting MED12 was lethal, with blood cell growth colonies dropping from an average of 25 per plate to five per plate in 10 days.

Further experiments showed that removing MED12 deactivated

enhancer components that normally help increase gene transcription and hematopoiesis.

Lead study investigator and NYU Langone associate research scientist Beatriz Aranda-Orgilles, PhD, says the team next plans to screen blood samples from cancer patients for signs of MED12 mutations and uncontrolled HSC development. The team also plans experiments to identify the biological mechanisms involved in MED12 hyperactivation, including how the complex binds to enhancer molecules to regulate blood cell maturation.

Aranda-Orgilles says the team has further goals to identify drug molecules that could block MED12 hyperactivity and serve as potential MED12 inhibitors.

More information: *Cell Stem Cell*, DOI: 10.1016/j.stem.2016.08.004

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