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Disease decoded: Gene mutation may lead to development of new cancer drugs

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The discovery of a gene mutation that causes a rare premature aging disease could lead to the development of drugs that block the rapid, unstoppable cell division that makes cancer so deadly.

Scientists at the University of Michigan and the U-M Health System recently discovered a protein mutation that causes the devastating disease dyskeratosis congenita, in which precious hematopoietic stem cells can't regenerate and make new blood. People with DC age prematurely and are prone to cancer and bone marrow failure.

But the study findings reach far beyond the roughly one in 1 million known DC patients, and could ultimately lead to developing new drugs that prevent cancer from spreading, said Jayakrishnan Nandakumar, assistant professor in the U-M Department of Molecular, Cellular, and Developmental Biology.

The DC-causing mutation occurs in a protein called TPP1. The mutation inhibits TPP1's ability to bind the enzyme telomerase to the ends of chromosomes, which ultimately results in reduced hematopoietic stem cell division. While telomerase is underproduced in DC patients, the opposite is true for cells in cancer patients.

"Telomerase overproduction in cancer cells helps them divide uncontrollably, which is a hallmark of all cancers," Nandakumar said. "Inhibiting telomerase will be an effective way to kill cancer cells."

The findings could lead to the development of gene therapies to repair the mutation and start cell division in DC patients, or drugs to inhibit telomerase and cell division in cancer patients. Both would amount to huge treatment breakthroughs for DC and cancer patients, Nandakumar said.

Nandakumar said that a major step moving forward is to culture DC patient-derived cells and try to repair the TPP1 mutation to see if telomerase function can be restored. Ultimately, the U-M scientist hopes that fixing the TPP1 mutation repairs telomerase function and fuels cell division in the stem cells of DC patients.

"It's conceivable that with the recent advancement in human genome-editing technology, we could, in the not-so-distant future, repair the mutation in hematopoietic stem cells in the bone marrow of DC patients," Nandakumar said.

The findings also reinforce how one tiny change in an amino acid chain can cause devastating health consequences.

"It was surprising to us that just deleting one single amino acid in a protein chain that is 544 amino acids long can result in such a severe disease," Nandakumar said.

More information: The study, "Hoyeraal-Hreidarsson syndrome caused by a germline mutation in the TEL patch of the telomere protein TPP1," appears in the journal *Genes and Development*. genesdev.cshlp.org/content/ear … .248567.114.abstract

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