Cardiovascular drug may offer new treatment for some difficult types of leukemia

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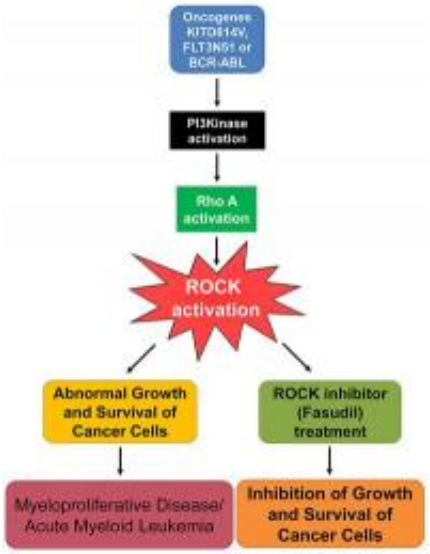

Mutations in several oncogenes activate Rho kinase (ROCK), which promotes abnormal growth of cancer cells and can lead to leukemia. Laboratory tests by a team lead by Indiana University School of Medicine scientists found that Fasudil, which targets ROCK, can inhibit the growth of the cancer cells. Credit: Indiana University School of Medicine

A drug now prescribed for cardiovascular problems could become a new tool in physicians' arsenals to attack certain types of leukemia that so far have evaded effective treatments, researchers say.

The drug, Fasudil, has been used to treat stroke patients because it is a vasodilator, meaning it dilates blood vessels. However, its potential in leukemia emerged because its method of action is blocking the activity of a protein called Rho kinase, or ROCK.

ROCK, which plays a role in a variety of cellular activities, attracted the attention of the national research team led by Reuben Kapur, Ph.D., Frieda and Albrecht Kipp Professor of Pediatrics at the Indiana University School of Medicine, as they were studying the effects of mutations in several other proteins that are associated with difficult-to-treat types of leukemia. Those mutations, experiments revealed, resulted in hyperactivation of ROCK. The group reported its findings in the Sept. 13, 2011 issue of the journal *Cancer Cell*, which was published online Sept. 12.

"There's been a push to identify targets that get revved up as a result of the mutations we find in the leukemia cells, and we found that ROCK appeared to be hyperactive. Fasudil is available and targets ROCK, but its possible effectiveness as an anti-leukemia agent had not been tested," Dr. Kapur said.

"Many of these leukemia patients are older, especially those with acute myelogenous leukemia, and they undergo extensive chemotherapy," said Dr. Kapur. "If we could find other ways of treating them that would be more tolerable, that would be useful for older populations."

Leukemia covers a broad range of diseases involving excess production of immature white blood cells. The research team investigated the ramifications of mutations in genes for two receptor proteins known as KIT and FLT3. They also studied the effects of BCR-ABL, a protein produced when parts of two chromosomes swap places, an abnormality that is associated with chronic myelogenous leukemia. KIT, FLT3 and BCR-ABL are known as oncogenes due to their potential to cause

cancer.

In each case, blood-producing bone marrow cells with the mutations all had hyperactivated levels of ROCK. The researchers then were able to slow the growth of those cells in laboratory tests by using the ROCK inhibitor, Fasudil. Similarly, the drug significantly prolonged the survival of laboratory mice with leukemia.

Further testing is necessary, but the investigators found the results promising, said Dr. Kapur.

"This drug could be fairly potent across the board with a lot of leukemias," he said. "Whether alone or in combination with existing therapies it could have a lot of potential."

Provided by Indiana University School of Medicine