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Multitasking meds: Scientists discover how drug for leukemia, psoriasis, may tackle vascular disease

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A drug that has been on the market for decades to treat leukemia and skin disorders such as acne and psoriasis may be a possible therapy for vascular diseases, including atherosclerosis and hypertension, which can lead to heart attack or stroke.

Previously, researchers discovered that retinoids – commonly used natural or man-made drugs related to vitamin A – blunted experimental vascular disease by spurring into action a very particular segment of a gene known for its ability to curb cancer cell growth.

The gene, usually shut off or silenced in cancer cells, enabling tumors to form, could be an attractive treatment target not only for vascular diseases, which involve the detrimental growth, spread and accumulation of cells in blood vessels, but for a wide range of cancers, which involve unchecked cell growth, as well.

In the journal *PLoS One*, a team of researchers led by Joseph M. Miano, Ph.D., associate director of the Aab Cardiovascular Research Institute at the University of Rochester Medical Center, found that a specific section of the complex AKAP12 gene, called AKAP12 beta, is extremely responsive to treatment with retinoids, and that ramping up its activity reduces vascular cell growth.

"Several studies have shown that when this gene is turned on, it

decreases the growth of cancer cells, but this is the first time anyone's shown its ability to inhibit growth in non-cancer cells," said Miano, the study's lead author. "In addition to the vascular angle, we hope this work inspires researchers in different disciplines to see if our findings apply in other disease contexts."

A vascular biologist, Miano became interested in retinoids after people close to him battled cancer. When he learned that retinoids, which have several actions, including regulating cell growth, were a treatment option for some cancer patients, he wondered if they might have any use in treating diseases of blood vessels. Like cancer, vascular diseases such as atherosclerosis – the narrowing of the arteries – involve excessive cell growth and invasion. Such activities can lead to blocked arteries that obstruct blood flow.

Miano decided to give the idea a try, and in the late 1990's he showed in tissue and in an animal model of vascular disease that retinoids inhibited the growth of smooth muscle cells, which are found within the walls of vessels and contribute to atherosclerosis, which can lead to heart attack or stroke.

In the early 2000's, his team identified a number of genes that were activated or turned on by retinoids, one of which was AKAP12. Because research in the cancer field suggested it was a tumor suppressor gene, named for its ability to hinder cancer cell growth, Miano honed in on AKAP12 to see if it might be a target of retinoids in the context of vascular disease.

The team discovered that AKAP12 is a very complex gene, with three distinct DNA segments, named AKAP12 alpha, beta and gamma. Miano noted, "It is essentially like having three genes in one." Gene expression analyses revealed that the treatment of damaged vessels with retinoids immediately stimulated AKAP12 beta into action, while the alpha and

gamma segments showed no response to the therapy.

"There are lots of tumor suppressor genes out there, and a few are mildly responsive to retinoids, but this is the first time we've seen a gene – AKAP12 beta – respond so early and so profoundly to retinoid stimulation," said Miano. "Without AKAP12 beta up and running, it is as if there are no brakes and the smooth muscle cells are free to grow. But when AKAP12 beta is amplified, the opposite is true, and we see major decreases in smooth muscle cell growth."

Once AKAP12 beta is switched into "go" mode by retinoids, the team believes it helps deter cell growth by reigning in and directing the action of specific signaling proteins that influence cell growth and migration. More research is needed to pin down the exact processes involved, and Miano hopes to pursue this work in the future by exploring animal models in which AKAP12 is eliminated or turned on with drugs.

According to Irwin H. Gelman, Ph.D., who was the first to identify the AKAP12 gene and has been studying its role in cancer for many years, "This study makes sense and is very consistent with what we've found in cancer cells, which is that AKAP12 is a prime driver to stop the proliferation of cells." Gelman, a study author who has worked with Miano for more than ten years, is the Palisano Chair of Cancer Genetics at Roswell Park Cancer Institute in Buffalo, New York.

"It may be possible that other diseases marked by inappropriate cell proliferation due to AKAP12 turn-off could also be reversed by retinoid treatment," added Gelman.

Provided by University of Rochester Medical Center

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