Gene offers an athlete's heart without the exercise

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Researchers at Case Western Reserve University have found that a single gene poses a double threat to disease: Not only does it inhibit the growth and spread of breast tumors, but it also makes hearts healthier.

In 2012, medical school researchers discovered the suppressive effects of the gene HEXIM1 on breast cancer in mouse models. Now they have demonstrated that it also enhances the number and density of blood vessels in the heart – a sure sign of cardiac fitness.

Scientists re-expressed the HEXIM1 gene in the adult mouse heart and found that the hearts grew heavier and larger without exercise. In addition, the animals' resting heart rates decreased. The lowered heart rate indicates improved efficiency, and is supported by their finding that transgenic hearts are pumping more blood per beat. The team also discovered that untrained transgenic mice ran twice as long as those without any genetic modification.

"Our promising discovery reveals the potential for HEXIM1 to kill two birds with one stone – potentially circumventing heart disease as well as cancer, the country's leading causes of death," said Monica Montano, PhD, associate professor of pharmacology, member of the Case Comprehensive Cancer Center, who created the mice for the heart and breast cancer research and one of the lead researchers.

Hypertension and subsequent heart failure are characterized by a mismatch between the heart muscles' need for oxygen and nutrients and

blood vessels' inability to deliver either at the rate required. This deficit leads to an enlarged heart that, in turn, often ultimately weakens and stops. The researchers showed that increasing blood vessel growth through the artificial enhancement of HEXIM1 levels improved overall function – HEXIM1 may be a possible therapeutic target for heart disease.

The study, published online in the peer-reviewed journal *Cardiovascular Research*, is the sixth from the team of Dr. Montano and Michiko Watanabe, PhD, professor of pediatrics, genetics, and anatomy at Case Western Reserve School of Medicine and director of Pediatric Cardiology Fellowship Research at Rainbow Babies and Children's Hospital. Their collaboration began in 2004 with an investigation of why mice expressing mutant HEXIM1 suffered heart failure in the fetal stages of life. The research team found then that the gene is important for cardiovascular development and that it is abundant in the earliest months of life. This discovery led the team to explore whether increasing HEXIM1 levels could help reverse cardiovascular disease by encouraging vessel growth.

"Our Cleveland-based collaborative research teams revealed that increasing HEXIM1 levels brought normal functioning hearts up to an athletic level, which could perhaps stand up to the physical insults of various cardiovascular diseases," Watanabe said.

The results build on the team's findings last year that showed increased levels of HEXIM1 suppressed the growth of breast cancer tumors. Using a well-known mouse model of breast cancer metastasis, researchers induced the gene's expression by locally delivering a drug, hexamethylene-bisacetamide using an FDA-approved polymer. The strategy increased local HEXIM1 levels and inhibited the spread of breast cancer. The team is currently making a more potent version of the drug and intends to move to clinical trials within a few years.

"Many cancer drugs have detrimental effects on the heart," said Mukesh K. Jain, MD, FAHA, professor of medicine, Ellery Sedgwick Jr. Chair and director of Case Cardiovascular Research Institute at Case Western Reserve School of Medicine. "It would be beneficial to have a cancer therapeutic with no adverse effects on the heart and perhaps even enhance its function."

The Case Western Reserve-led research team is now investigating HEXIM1's ability to improve the health of mice with cardiovascular disease. They are investigating the drug's ability to reduce the damage from heart attacks.

Provided by Case Western Reserve University