MedicalXpress

Cancer-related pathways reveal potential treatment target for congenital heart disease

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(PhysOrg.com) -- Cross-disciplinary teams of scientists studying genetic pathways that are mutated in many forms of cancer, but which also cause certain forms of congenital heart disease, including hypertrophic cardiomyopathy (HCM), have introduced these mutations into mice and successfully treated HCM in the lab.

In two separate but related studies in Toronto, and Boston, the scientists proved that two drugs - one already approved as an immunosuppressant, the other being tested as an anti- cancer agent- could prevent and reverse HCM -- a thickening of the heart muscle that is the leading cause of sudden death in children and young adults -- in mouse models of congenital heart disease.

The research findings are published online Feb. 21 ahead of the March issue of the Journal of Clinical Investigation.

Both studies were co-led by Benjamin Neel, a Professor in the Department of Medical Biophysics at the University of Toronto, Canada Research Chair in Cell Signalling. Neel is also director of the Ontario Cancer Institute, which includes The Campbell Family Cancer Research Institute and is based at the University Health Network.

“By studying two of the most commonly mutated pathways in cancer, discerning the mechanism by which they cause congenital disease, and treating two of these disorders with different drugs, we have identified potential therapeutic targets for human disease,” said Neel. “This is what

personalized medicine is all about: understanding in detail how different mutations cause disease, and then targeting these mutations appropriately to tailor individualized treatment."

He added: "These findings exemplify the importance of basic biological research and collaboration across areas of specialization. In this instance, collaboration showed how understanding cancer can lead to unexpected insights into congenital heart disease, and vice versa."

The scientists were investigating how a cluster of congenital diseases known as "RASopathies" - defects caused by mutations in different genes in the so-called "RAS pathway" - develop. They focused on two genetic disorders: Noonan Syndrome, which occurs in 1 in 1,000-2,500 live births and causes short stature, facial, blood and cardiovascular abnormalities; and the much less common LEOPARD Syndrome, which features short stature, as well as skin, facial, skeletal and cardiovascular abnormalities. HCM is prevalent in both syndromes.

The UHN study team, co-led by Dr. Toshiyuki Araki, assistant scientist at the Campbell Family Institute, and Dr. Peter Backx, U of T professor of physiology and a senior scientist at Toronto General Research Institute and the Peter Munk Cardiac Centre, investigated Noonan Syndrome. The Boston team, led by Dr. Maria Kontaridis, assistant professor of medicine at Harvard Medical School and Division of Cardiology, BIDMC, investigated LEOPARD Syndrome.

The scientists introduced the genetic mutations that cause these syndromes into special strains of mice, and were able to reproduce the features of the human disorders. The Toronto group found that "excessive activity of an enzyme called ERK, a downstream target of the RAS pathway, caused HCM in Noonan Syndrome, and successfully used a drug that lowers the activity of this enzyme to decrease pathway activity and normalize all of the features of Noonan Syndrome," says Dr.

Neel. The Boston group found that LEOPARD Syndrome results from excessive activity of a different enzyme downstream of RAS, called mTOR. Using the mTOR inhibitor Rapamycin, which is already approved as an immunosuppressant, they were able to reverse HCM in their mouse model of LEOPARD Syndrome.

“These research findings are important steps towards understanding the pathogenesis of these congenital syndromes, and point the way toward clinical trials of these agents in severely affected patients,” said Neel.

Provided by University of Toronto