Growth factor hit by cancer drugs also protects heart

January 11 2010

A growth factor that is a common target of cancer drugs also plays an important role in the heart's response to stress, researchers at The University of Texas M. D. Anderson Cancer Center report online this week in the *Journal of Clinical Investigation*.

In many cancers, the body makes too much platelet-derived growth factor receptor (PDGFR), a type of protein that controls cell growth, allowing cancer cells to increase uncontrollably. Several chemotherapy agents, including Sutent(r) (sunitinib), Nexavar(r) (sorafenib) and Gleevec(r) (imatinib), work by targeting and inhibiting PDGFR. This slows the growth of cancer - as well as angiogenesis, which is the growth of new blood vessels.

"Recently, some of these targeted anti-cancer drugs have been associated with heart failure," said Aarif Khakoo, M.D., assistant professor in M. D. Anderson's Department of Cardiology and corresponding author on the study, said. "But the role of PDGFR signaling in the heart has been largely unexplored until now."

In this study, Khakoo and his colleagues showed that, while PDGFR-inhibiting agents may slow the growth of cancer cells, they also may impair the heart's ability to respond to stress. Since these agents also often cause elevated blood pressure, this causes a double bind of added stress to the heart and lessened capacity to deal with this stress.

Limiting PDGFR causes heart failure in mice

Using special laboratory mice with limited cardiac PDGFR and mice with normal PDGFR signaling, researchers performed transverse aortic constriction (TAC), a procedure widely used to study heart disease in which a band is placed at the aortic arch, resulting in acute pressure overload. The mice with limited PDGFR had heart failure.

"We showed that cardiomyocyte PDGFR expression and activation in heart muscle cells rises dramatically in response to pressure overload stress," Khakoo said. "Furthermore, we showed that knockout of PDGFR in heart muscle results in cardiac dysfunction, heart failure and a marked defect in stress-induced cardiac angiogenesis."

They also demonstrated that PDGFR signaling is crucial in the creation of new blood vessels that help the heart respond to stress.

High blood pressure may put patients who receive these drugs at even greater risk.

"Since these drugs also cause vascular stress in the form of severe high blood pressure in a significant numbers of patients, our findings suggest the double hit of high blood pressure and the blockade of PDGFR signaling may play a key role in heart problems when patients are treated with anti-cancer agents whose targets include PDGFR," Khakoo said.

Khakoo said the study suggests aggressive control of high blood pressure may significantly reduce cardiac toxicity caused by these agents.

Moving forward, delving deeper

This study opens the door to studying additional effects of PDGFR-

inhibiting drugs on the heart, as well as ways to prevent damage to the heart.

"Patients with pre-existing heart disease may be at increased risk for cardiomyopathy and heart failure associated with these drugs," Khakoo said. "If we can confirm this, it might help develop a tool to determine the individual risk for cancer patients being considered for treatment with PDGFR inhibitors and to develop strategies to prevent heart damage."

Provided by University of Texas M. D. Anderson Cancer Center