Certain anticancer agents could be harmful to patients with heart disease

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A set of promising new anticancer agents could have unforeseen risks in individuals with heart disease, suggests research at Washington University School of Medicine in St. Louis. The anticancer drugs — which go by the strange name of hedgehog antagonists — interfere with a biochemical process that promotes growth in some cancer cells. But the researchers showed that interfering with this biochemical process in mice with heart disease led to further deterioration of cardiac function and ultimately death.

"This finding should serve as a warning that these drugs might have adverse effects on the heart and that it could be very important to monitor patients' cardiovascular health when using this type of anticancer drug," says senior author David Ornitz, M.D., Ph.D., the Alumni Endowed Professor and head of Developmental Biology. The research was reported June 20, 2008, in advance online publication in the *Journal of Clinical Investigation*.

Hedgehog antagonists are drugs that inhibit the hedgehog signaling pathway, a chain of biochemical signals that regulate cellular growth and differentiation. The odd term hedgehog has little to do with the small, spiny mammals — it originated when scientists noted the spiky, hedgehog-like appearance of fly embryos with abnormal hedgehog genes. Every organism in the animal kingdom has hedgehog genes, which play an essential role in guiding cells to mature into the appropriate form for proper function.

Ornitz and his research team, including lead author Kory Lavine, M.D., Ph.D., now a resident in the Cardiovascular Division of the Department of Medicine at Washington University School of Medicine, are on the forefront of research into how blood vessels in heart muscle develop in growing embryos. They recently found that the hedgehog signaling pathway was vital to the development of the heart's blood supply.

Now the Washington University research team has demonstrated that the hedgehog signaling process is important not just in the early development of the heart, but also in adult hearts — to maintain cardiac blood vessels. They found that completely blocking hedgehog signaling in the hearts of adult mice caused many small coronary blood vessels to disappear, leaving heart muscle short of oxygen and leading to heart failure. In mice with experimentally induced heart attacks, mildly inhibiting hedgehog signaling led to a worsening of their heart conditions.

"We gave mice small amounts of antibodies against hedgehog, and in those that had a recent myocardial infarction (heart attack), this led to poorer heart function and some lethality," explains Lavine. "We've shown that small decreases in the hedgehog pathway in the setting of heart disease can lead to deleterious outcomes, and since a number of patients with cancer also have heart disease, this raises concern for those who might be treated with hedgehog antagonists."

Studies suggest that abnormal activation of the hedgehog pathway is implicated in many different types of cancer, and drugs that impede hedgehog signaling are being tested against several of these cancers, including basal cell carcinoma (a type of skin cancer), prostate cancer, pancreatic cancer, colorectal cancer and medulloblastoma (a type of brain tumor). These trials are still in the early stage.

The current study was the first demonstration that hedgehog signaling is

essential to maintain a healthy supply of blood vessels in heart muscle in adult organisms.

"Nobody had ever looked for hedgehog signaling in the adult heart before," says Ornitz. "Kory discovered that the hedgehog signaling pathway is a mechanism to regulate the heart's vasculature by influencing growth factors that promote blood vessel growth. The body can tune the hedgehog pathway to modulate its signal and increase and decrease blood vessels on demand, providing a mechanism to ensure a constant supply of oxygenated blood for the energy-hungry cells of heart muscle."

The researchers say that the role of hedgehog signaling in the vasculature of the heart means that it could be a target for new drugs that could be used to treat heart disease. Ornitz says the study also suggests that hedgehog signaling could be required to maintain blood vessels elsewhere in the body. That means it could also be uniquely important in the brain, which has a very dense capillary network, and that drugs that increase hedgehog signaling could possibly be useful to treat strokes. Lavine, who has just graduated from the Washington University Medical Scientist Training Program will begin an internal medicine cardiology residency and cardiovascular diseases fellowship. He plans to investigate the contribution of hedgehog signaling in other forms of heart disease such as diabetic cardiovascular disease.

Source: Washington University School of Medicine