MedicalXpress

Study explains how heart attack can lead to heart rupture

November 17 2011

For people who initially survive a heart attack, a significant cause of death in the next few days is cardiac rupture -- literally, bursting of the heart wall.

A new study by University of Iowa researchers pinpoints a single protein as the key player in the biochemical cascade that leads to cardiac rupture. The findings, published Nov. 13 as an Advance Online Publication (AOP) of the journal Nature Medicine, suggest that blocking the action of this protein, known as CaM kinase, may help prevent cardiac rupture and reduce the risk of death.

After a heart attack, the body produces a range of chemicals that trigger biological processes involved in healing and repair. Unfortunately, many of these chemical signals can become "too much of a good thing" and end up causing further damage often leading to heart failure and sudden death.

"Two of the medicines that are most effective for heart failure are beta-blockers, which block the action of adrenaline, and drugs that block the angiotensin receptor," explains Mark E. Anderson, M.D., Ph.D., UI professor and head of internal medicine and senior study author. "The third tier of therapy is medication that blocks the action of aldosterone."

Aldosterone levels increase in patients following a heart attack, and higher levels of the hormone are clearly associated with greater risk of death in the days immediately following a heart attack.

Increased aldosterone levels also are associated with a burst of oxidation in heart muscle, and in 2008, Anderson's team showed that oxidation activates CaM kinase. Anderson's research has also shown that CaM kinase is a lynchpin in the beta-blocker and angiotensin pathways.

"We wondered if aldosterone might somehow work through CaM kinase and, if it did, could some of the benefits of aldosterone blockers be attributed to effects on CaM kinase?" Anderson says.

Anderson's team, including co-first authors Julie He, a student in the UI Medical Scientist Training Program; Mei-Ling Joiner, Ph.D.; Madhu Singh, Ph.D.; Elizabeth Luczak, Ph.D.; and Paari Swaminathan, M.D., devised a series of experiments in mice to investigate how elevated levels of aldosterone damage heart muscle after a heart attack and how Cam kinase is involved.

The experiments confirmed that aldosterone increases the amount of oxidized, and therefore, activated CaM kinase in heart muscle. Mice given excess aldosterone, mimicking levels seen in human patients, were twice as likely to die after a heart attack as mice that were not given extra aldosterone (70 percent vs. 35 percent), and the cause of death was heart rupture.

Importantly, any treatment that reduced the amount of oxidized CaM kinase or otherwise inhibited CaM kinase activity lowered the risk of cardiac rupture and death in the mice.

Interestingly, the researchers found that activated CaM kinase prompted heart muscle cells to produce an enzyme called MMP9 that is implicated in heart rupture.

"Although there are many sources of this enzyme, our study showed that heart muscle itself is actually making this protein too and is acting

against its own self-interest in doing so," Anderson says. "We don't know why it happens, but inhibiting CaM kinase can prevent it."

The MMP9 enzyme is involved in remodeling the "matrix" that surrounds heart cells. This matrix, which acts like mortar between cells, is constantly being broken down and rebuilt. In hearts that rupture after heart attack this remodeling process becomes excessive, weakening the matrix to the point that it ruptures.

Because matrix remodeling plays a role in other diseases, including cancer, Anderson notes that the CaM kinase findings may have clinical implications beyond heart disease.

Overall, the UI study suggests that blocking the biochemical processes triggered by aldosterone might help prevent cardiac rupture following a heart attack.

Anderson notes that a multi-center study currently underway in France is poised to determine if patients would benefit from getting aldosterone blockers right away rather than waiting several weeks.

"We think our study provides experimental evidence for why that should work," he says.

"We have now identified CaM kinase as a critical component for the disease effects of the three core therapeutic pathways in heart, and we are closer to understanding fundamental elements of these signaling pathways," Anderson says. "The findings enhance excitement that CaM kinase might be an important therapeutic target in heart disease, and developing Cam kinase inhibitors is a major goal for us so that we can move this from experimental findings to clinical testing."

Provided by University of Iowa Health Care