Molecule involved in heart failure now implicated in heart attack damage

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A molecule known to be involved in progressive heart failure has now been shown to also lead to permanent damage after a heart attack, according to researchers at Thomas Jefferson University.

To prove this novel conclusion, the research team used gene therapy to inhibit the small protein, kinase known as G protein-coupled receptor kinase 2 (GRK2), and found heart muscles cells in mice were substantially protected against destruction that would otherwise occur after an induced myocardial infarction (MI), or heart attack.

Conversely, mice engineered to express excess GRK2 had more damage than would have been expected after an MI, the researchers say in the article currently found online at Circulation Research and to be published in the October 29th issue.

These finding suggest that humans experiencing a heart attack might be helped with delivery of a therapeutic targeting inhibition of GRK2, says Walter J. Koch, Ph.D., Director of the Center for Translation Medicine at Jefferson.

"Our results clearly show that GRK2 promotes cell death after a heart attack, so an inhibitor of this molecule is likely beneficial in preventing permanent damage, if delivered quickly enough," he says. "Currently, we have a gene therapy approach but for this indication a small molecule would be preferred."

Dr. Koch says that while it may be years before this concept can be tested in patients experiencing an MI, he expects anti-GRK2 gene therapy will be tested in patients with heart failure much sooner. A Phase I clinical trial for GRK2-targeted gene therapy is preparing to be launched, pending federal approval.

Dr. Koch and his colleagues have been working for 15 years to link GRK2 to heart failure in patients. They have demonstrated that the protein puts a brake on the beta-adrenergic receptors that respond to hormones (adrenalin and noradrenalin) that drive the heart beat - the rate and force of contractile function in heart cells. This braking action is enhanced in chronic heart failure, and relieving it by inhibiting activity and expression of GRK2 allows the heart to work better, the researchers have shown in animal studies using gene therapy.

The question they looked at in this study is whether GRK2 plays any role after a heart attack. Most cardiology researchers theorized that it was protective, because expression of the protein is increased by three to four times immediately after a heart attack, Dr. Koch says. "People always thought that GRK2 was working to shut off beta receptors because injured hearts were pumping out too much adrenaline, and that this blocking of over activity in an injured heart is protective."

But what the researchers discovered is that over production of GRK2 following a heart attack actually stimulates pro-death pathways in myocyctes (heart cells) outside of the initial zone of damage. They specifically found an inverse link between GRK2 activity and the production of nitric oxide (NO), a molecular messenger that protects the heart against damage caused by a sudden loss of blood. "When there is more GRK2, there is less NO, and vice versa," Dr. Koch says. They believe that GRK2 may be affecting NO production by inhibiting the prosurvival protein kinase Akt, which itself regulates NO. (more)

The mice MI studies then proved that inhibiting GRK2 protected heart cells, Dr. Koch says.

"Our results clearly show that GRK2 is a pathological target in the heart, involved in both progressive heart failure and in death of heart cells after a heart attack," he says.

Provided by Thomas Jefferson University

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