Protein tug of war points toward better therapies for cardiovascular disease

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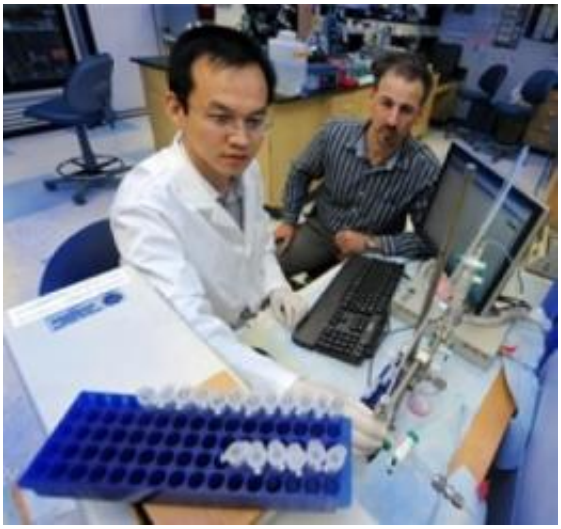

Drs. Fulton and Chen's finding indicates an antiulcer drug just may help the body reduce excessive levels of superoxide, a highly reactive and potentially destructive product of oxygen that's dramatically elevated in cardiovascular disease. Credit: Photo by Phil Jones, Georgia Health Sciences University Photographer

Two proteins are in a tug of war that determines how much the body makes of superoxide, a highly reactive and potentially destructive product of oxygen that's dramatically elevated in cardiovascular disease, researchers report.

Their finding indicates an antiulcer drug just may help the body reduce

excessive levels.

Hsp90 and Hsp70 are both heat shock proteins but appear to have opposite effects on reactive oxygen species production, said Dr. David J.R. Fulton, Interim Director of the Vascular Biology Center at the Medical College of Georgia at Georgia Health Sciences University.

"Our studies show that Hsp90 promotes the activity of Nox enzymes, the source of reactive superoxide and all of the reactive oxygen species that descend from it, while Hsp70 has an opposing action that inhibits Nox," Fulton said.

When researchers gave Hsp90 inhibitors, the binding of Nox enzymes to Hsp90 was reduced, its binding to Hsp70 increased and reactive oxygen species production decreased. The inhibitors also reduced reactive oxygen species production in blood vessels from obese mice, where it contributes to the loss of elasticity and narrowing that are hallmarks of cardiovascular disease. While Hsp90 inhibition was known to suppress inflammation and reduce cardiovascular damage, just how it made these positive changes was unknown.

The yin and yang the researchers found points toward a targeted therapy that should give Hsp70 the edge, said Dr. Feng Chen, postdoctoral fellow. Chen is first author of the study in the American Heart Association journal *Arteriosclerosis, Thrombosis and Vascular Biology*.

Hsp90 inhibitors are used to treat cancer, which depends on Hsp90 to support rapid cell division. But they also target proteins that help blood vessels relax, such as nitric oxide synthase, so probably are not a good choice in cardiovascular disease. "Cardiovascular disease is a chronic disease, and we want to minimize negative side effects while providing protection," Fulton said.

In this case, a better approach appears to be directly increasing the expression of Hsp70 with a drug such as geranylgeranylacetone, or GGA, an antiulcer drug used in Japan with relatively few side effects, Chen said. When the MCG researchers treated human aortic vascular smooth muscle cells with the drug, for example, Hsp70's binding to Nox increased while Nox's ability to generate superoxide decreased.

Next steps include looking at whether this increased expression of Hsp70 actually translates to healthier blood vessels in a cardiovascular model. "If we can upregulate Hsp70 without affecting nitric oxide synthase, it should," said Fulton, the study's corresponding author.

Hsp70 and 90 are chaperones that guide protein folding in different ways and can influence more than just whether Nox enzymes are stable or degraded. Hsp70 levels are regulated by the molecule heat shock factor, which is bound to and repressed by Hsp90. That's one reason why Hsp90 inhibitors increase Hsp70 levels.

Reactive oxygen species are not all bad, the researchers noted. At normal levels, they aid cell signaling and homeostasis as well as the mounting of an immune response. However, excessive levels associated with chronic inflammation are thought to accelerate cardiovascular disease. "A little bit is good; you want a well-honed immune system to fend of pathogens," Fulton said. "Chronic inflammation is the problem."

The researchers completed their studies in normal and diabetic mice – diabetes increases the risk of cardiovascular disease by at least 50 percent – as well as the saphenous, or major superficial leg veins, of patients with cardiovascular disease.

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