A small molecule may help reduce damage in aging-related heart attacks

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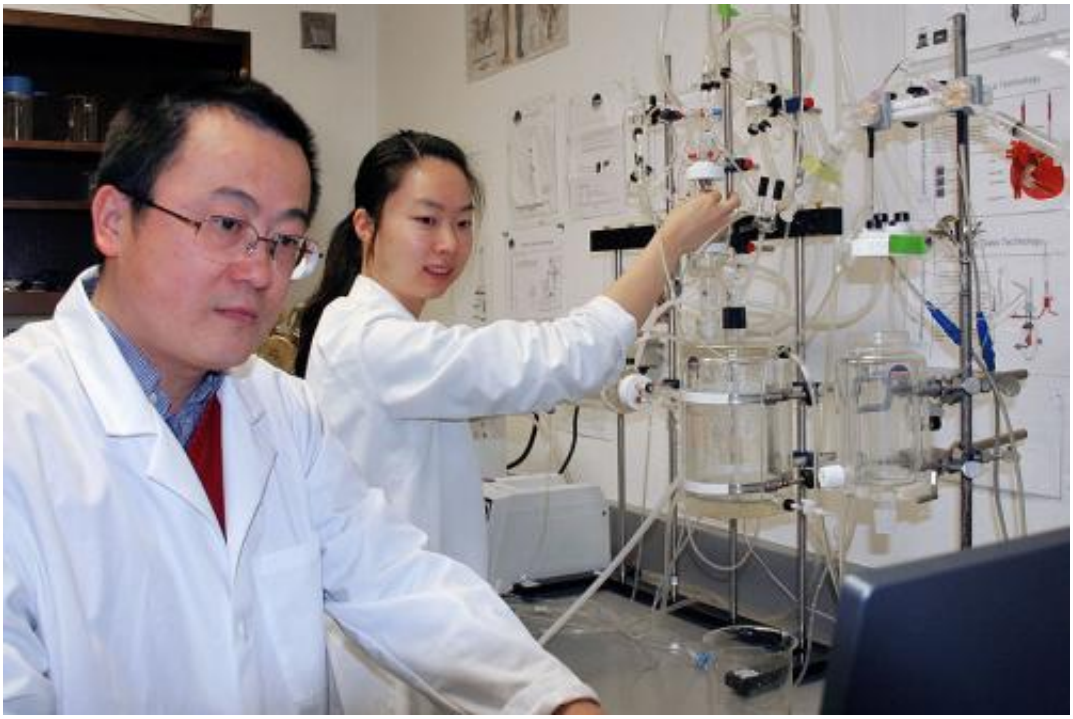

Research by UB assistant professor of pharmacology and toxicology Ji Li (left) and Jingying Wang, formerly of Li's lab, with collaborators at Yale, may result in a novel approach to reduce the severity of heart attacks in the elderly.

(Medical Xpress)—A small molecule developed at Yale University to limit damage done by ischemia – restricted blood flow – during heart attacks or surgery has been shown to reduce by 40 percent the amount of heart muscle damaged by myocardial infarction in animal studies by University at Buffalo pharmacologists.

Published last month in *Circulation* and online in June, the translational medicine research conducted by the UB-Yale team signals a new approach to limiting ischemic injury and possibly reducing the severity of heart attacks in the elderly.

The team has been collaborating since 2007, when Ji Li, PhD, assistant professor of pharmacology and toxicology in the UB School of Medicine and Biomedical Sciences, was on the faculty in Yale's Department of Medicine.

Together with Richard Bucala, MD, PhD, of Yale, who led the current study, the UB-Yale team had previously published in *Nature* that the regulatory protein, MIF, (migration inhibitory factor) activated AMPK (AMP-activated protein kinase) to initiate a key cardioprotective pathway in the heart. The *Nature* study, performed in the laboratory of Yale professor of cardiology Lawrence H. Young, demonstrated that this signaling cascade was under genetic control and could be pharmacologically targeted for ameliorating the severity of ischemic heart disease.

In 2010, the UB-Yale team also published work that MIF action decreases in aging, hypothesizing that aging is associated with a decline in the ability of the heart to activate the MIF-AMPK signaling cascade in response to ischemia.

"That work showed us why myocardial infarction is so common in the elderly, after age 70," Li explains. "Myocardial infarction occurs most commonly in this population."

The UB and Yale researchers continued their work when Yale chemists led by William L. Jorgenson, identified a small molecule, MIF20, that was shown by the Bucala group to increase MIF action through its receptor. Yale has filed patent applications on small molecule MIF

modulators to facilitate their pharmacologic development.

"We can't easily increase the level of protein in the elderly, but we can use this molecule to enhance AMPK activation," Li says. He explains that the small molecule, MIF20, acts to increase the binding between MIF and its cardiac receptor to optimally activate the cardioprotective pathway.

Li's group performed the key animal studies to demonstrate the utility of the small molecules discovered by the Yale researchers.

"Our data clearly show that in mice treated with MIF20, there was a 40 percent reduction in dead myocardium when compared to mice that hadn't been treated," he says.

The research shows that the small-molecular MIF agonists may offer a novel approach in selected clinical settings to compensate for age-related or genetic deficiencies in the way that the AMPK responds to ischemic injury, the researchers conclude.

"These pharmacological interventions that restore MIF-AMPK signaling in the aged heart may be a useful means to reduce cardiac damage caused by ischemic injury in older individuals," says Li.

The next step will be to replicate the findings in larger mammals.

Provided by University at Buffalo

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