'Danger' molecules may increase cardiovascular risk from early life stress

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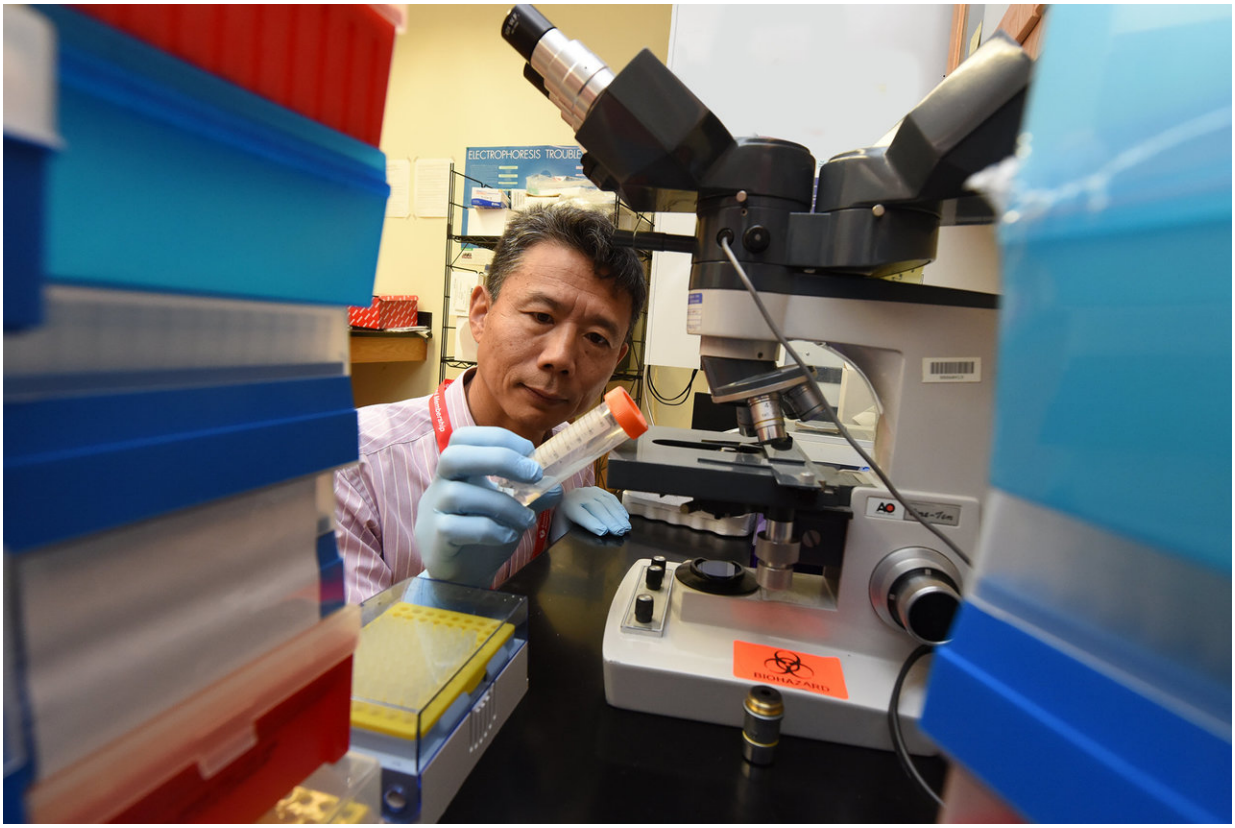

Dr. Yanbin Dong, geneticist and cardiologist at the Georgia Prevention Institute at the Medical College of Georgia at Augusta University. Credit: Phil Jones, Senior Photographer, Augusta University

The release of "danger" molecules in response to significant periods of

mental stress early in life may leave young people at lifelong risk of cardiovascular disease, scientists report.

"We know mental stress is bad for the cardiovascular system," says Dr. Yanbin Dong, geneticist and cardiologist at the Georgia Prevention Institute at the Medical College of Georgia at Augusta University. "We want to know more about how it's bad."

They think one answer is DAMPs, or damage (AKA "danger") associated molecular patterns. Stressed and dying cells regularly empty their contents, or DAMPs.

"Their job is to signal your body that there is danger and to do something about it," says Dong, including triggering inflammation, which can both help eliminate an invader and heal. DAMPs help heal a knife wound to the chest, for example. But at a certain point, the body has mechanisms to eliminate what becomes inflammation-producing trash. And there is increasing evidence that high DAMP levels for extended periods can overwhelm that natural system, which can lead to chronic inflammation and a host of associated health problems, including cardiovascular disease.

Dr. Clinton Webb, Herbert S. Kupperman Chair in Cardiovascular Disease in the MCG Department of Physiology, is leading another major research initiative looking at how high blood pressure, for example, results in more cell death which results in more DAMPs being dumped which fuels inflammation and high blood pressure.

"We know that mental stress has a physiological impact, which includes things like transiently increasing your heart rate and blood pressure. Would DAMPs also be involved in the mental stress process? That is my question," says Dong.

His hypothesis is that, like with high blood pressure, significant mental stress also creates a vicious cycle by stressing cells and elevating DAMPs, inflammation and blood pressure.

If he is right, "DAMPs might be a good target to reduce the impact of mental stress on our physical wellbeing," Dong says.

Blood pressure generally tracks from childhood into adulthood. And, early life stress, from parents who are socioeconomically challenged, to actual adverse child events, or ACEs, like sexual abuse and neglect, already are associated with hypertension in adulthood, potentially even hastening its development.

A 2015 study in the journal *Circulation* led by Dr. Shaoyong Su, genetic epidemiologist at the Georgia Prevention Institute and a co-investigator on the new study, showed that children who experience multiple ACEs, already have higher blood pressures as young adults.

A $2.4 million grant from the National Heart, Lung, and Blood Institute is helping Dong and his colleagues determine if DAMPs are a key factor.

They are looking again at data on about 400 study participants, on whom they have detailed measures of adverse childhood events. About 30 percent of those participants reported the moderate to severe life stresses that are a focus of this study. The now young adults are part of the Georgia Stress and Heart Study exploring risk factors for children to grow up as adults with heart disease, which gathered cardiovascular relevant information up to 17 times over 27 years, including periodic blood samples.

This time the scientists are correlating what reported stress does to DAMP levels in that blood. A pilot study in 14 of the

participants—some who reported significant psychological stressors and others who did not—indicated DAMP levels do increase with stress, although blood pressure increases were not significant, at least in that small cohort, Dong says.

The investigators are now further mining the information, looking at levels of three DAMPs known to stimulate inflammation, high-mobility group box 1, or HMGB1, one of the most studied DAMPs; as well as mitochondrial DNA; and heat shock protein 60, or HSP60.

High levels of circulating HMBG1 are an established cardiovascular risk associated with bodywide inflammation, organ damage and an increased risk of dying in patients with sepsis and an acute lung injury. But their role in hypertension remains unclear.

Mitochondria, which produce fuel for cells, have DNA that is distinctive from our own, so when it spills because of stress of injury, it's known to also prompt an inflammatory response. Early life stress increases oxidative stress and mitochondrial damage but studies have not been done to determine if mitochondrial DNA levels remain elevated.

HSP60 is a member of a family of proteins typically associated with protecting cells from stress, but associated as well with a variety of diseases, including cancer. HSP60, which is known to aid the replication of mitochondrial DNA, also has been associated with inflammation, low socioeconomic status, social isolation and psychological stress, and elevated levels have been found in patients with borderline hypertension. However, long-term impact on blood pressure is unknown, the investigators say, and their study is the first to examine the link between elevated HSP60 and early life stress, Dong says.

They are looking retrospectively at what happens to blood levels of those DAMPs over time and what routine and 24-hour blood pressure checks

indicate at those times. They also are looking at what happens to other factors, like how much blood pressure reacts to a stressor in real time, which gets mixed reviews as to whether it's good or bad in terms of cardiovascular risk, as well as established risks like arterial stiffness, a thickened carotid artery wall and the size of the pumping chamber of the heart. A larger ventricle means the heart is having to work hard to pump blood against higher resistance in blood vessels.

They want to know if DAMPs are involved in an increased cardiovascular risk over time and whether race or gender influence their impact. Another question the investigators want to answer is whether repeated and/or ongoing psychological stress can get and keep DAMP levels up.

Related rat studies indicate that blocking DAMPs may reduce blood pressure increases that result from psychological stress.

The scientists hope to emerge at the end of the studies with new, targeted prevention and treatment strategies that can do the same for young people. Higher blood levels of DAMPs in childhood may also serve as a biomarker for future cardiovascular risk, Dong says.

"Particularly when you think of the physiological consequences, like hypertension or stroke, heart attack, kidney damage, we think you should put DAMPs in the picture," Dong says.

Early life stress can result in increased inflammation—a contributor to many diseases from high blood pressure to cardiovascular disease and cancer—that persists in adulthood, Dong says.

Childhood blood pressures in the country are generally edging upward. A study from 1988-2000 showed the top number, or systolic blood pressure, an indicator of the pressure against your artery wall when the

heart beats, edged up 1.4 points. The bottom number, or diastolic blood pressure measure, which indicates pressure between beats, moved up 3.3 points, according to a 2004 report in the *Journal of the American Medical Association*. Elevated levels of either are a factor in diagnosing high blood pressure and increased cardiovascular risk, according to the American Heart Association. Studies at institutions like MCG's Georgia Prevention Institute have shown that blood pressure levels track from childhood to adulthood, Dong says.

Provided by Medical College of Georgia at Augusta University