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Doubling down on heart failure: Researchers discover new route to disease, and drugs to match

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A new study in the journal *Circulation* packs a powerful one-two punch in the fight against heart failure. The leading blow: Identification of a unique alliance of proteins that plays a major role in the development of the disease. The second but equally powerful hit: Drugs that interfere with this axis already exist.

Though still in its infancy, the combination is just the type of research the scientific community is looking for in its efforts to speed up the development of the next generation of treatments for the nation's biggest killers, of which heart disease is the long-reigning champ.

Burns C. Blaxall, Ph.D., FAHA, of the University of Rochester Medical Center, led the research team to the discovery, which revolves around adrenaline, the hormone that regulates rate and strength of the heart and causes our hearts to beat furiously in a crisis. Adrenaline levels are constantly ramped in people with heart failure – the body's attempt to recharge a weakened heart. While decades of research have established a connection between elevated adrenaline and heart failure, there is still much to learn about how it contributes to the disease.

In a mouse model of heart failure, Blaxall's team found that chronically high levels of adrenaline spur a bad actor – a protein called PAR1 – into gear. Several years ago, collaborative work in Blaxall's laboratory showed that over-stimulating PAR1 in cardiac muscle cells leads to heart

failure, while blocking it protects against the disease.

But, like most processes in the body, adrenaline doesn't drive PAR1 on its own; the team discovered it tags a middleman – another protein, called MMP-13 – which then prompts activation of PAR1 to wreak havoc in the heart.

"This research is very exciting because we've identified a completely new pathway activated by adrenaline that contributes to heart failure," said Blaxall, an associate professor at the Aab Cardiovascular Research Institute at the Medical Center.

Even more exciting, the team demonstrated that targeting either protein in the pathway – removing PAR1 or inhibiting MMP-13 – prevented cardiac dysfunction in mice, suggesting that drugs directed at either may hold promise for the treatment of heart disease.

"Our idea going forward is that in addition to blocking the effects of adrenaline, which is what beta blockers were designed to do, it may be wise to also inhibit MMP13, or PAR1, or both, to help patients with heart failure," noted Blaxall.

Potential drug candidates are already available. Inhibitors of MMP-13 are currently under evaluation, mostly as a potential treatment for rheumatoid arthritis and osteoarthritis, where MMP-13 has been shown to play a role in the development of each condition. Additionally, drugs that block PAR1 have been tested as antiplatelet agents – drugs that stop blood clots from forming – in large-scale clinical trials.

Blaxall says that in the future he plans to test drugs like these in animal models of heart failure.

This strategy is in line with work being done by the National Center for

Advancing Translational Sciences (NCATS) at the National Institutes of Health, established in 2011 to address the gap between basic research findings and new treatments for patients. The center is encouraging researchers to focus on compounds that have already cleared key steps in the development process, including safety testing, as they work to develop new therapies.

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