Study uncovers mechanism behind virus-induced heart inflammation, suggests potential therapeutic target

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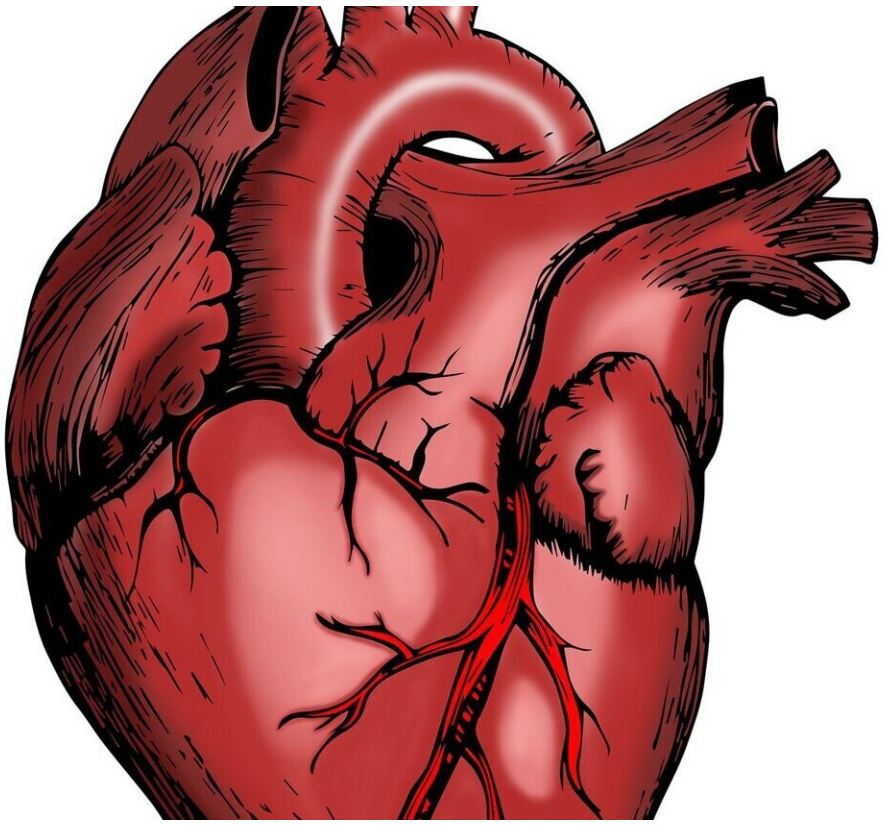

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A virus that attacks heart tissue wreaks havoc by triggering an inflammatory response that can ultimately lead to cell death. Now, a

team of scientists from Singapore and Canada has uncovered the role of a pathogen-detecting sensor in this response and demonstrated that targeting it might prevent progression to heart failure.

Typically, inflammation is a protective response that helps get rid of invading pathogens through a variety of immune responses. Among these are a large family of sensors, called nucleotide binding and oligomerization leucine rich repeat-containing proteins (NLRPs), which activate a cascade of inflammation-inducing molecules, called inflammasomes. However, sometimes these pathways can be hijacked by pathogens with damaging consequences.

Chronic inflammation of the blood circulatory system is widely implicated as a trigger for certain heart disorders, but little is known about the components involved in this inflammatory response. A better understanding of the types and roles of the NLRPs and inflammasomes in the heart could lead to new treatments that stop infections from progressing to heart failure.

"Our study sought to define the NLRP composition in heart muscles and the cells that line cardiac blood vessels," said the study's senior author, Assistant Professor Lena Ho, from the Cardiovascular and Metabolic Disorders (CVMD) Program at Duke-NUS Medical School, Singapore.

Asst Prof Ho, together with senior co-author Assistant Professor Franklin Zhong from the Lee Kong Chian School of Medicine (LKCMedicine) at Nanyang Technological University, Singapore, and colleagues from the University of British Columbia, Canada, and the Agency for Science, Technology and Research (A*STAR), Singapore, were able to determine that two NLRP sensors, called NLRP1 and CARD8, are the most important in the heart.

Not much is known about CARD8, but the team discovered that a virus

called Coxsackievirus B3 (CVB3) activates a chronic inflammatory response via this sensor. CVB3 is the most common cause of viral myocarditis: inflammation in the heart that can sometimes progress to cardiomyopathy and heart failure. CVB3 uses two of its proteins to cleave parts of CARD8, triggering an inflammatory process that allows the virus to continue replicating, damaging heart cells.

"We found that inactivating CARD8 protects heart and blood vessel cells from the inflammatory effects of CVB3 infection, raising the possibility that targeting CARD8 would be a viable strategy to prevent non-resolving CVB3 infections from progressing to heart failure," said Asst Prof Ho.

The team is now looking for ways to target CARD8 in cardiovascular inflammation and heart diseases and is further investigating this sensor to understand how it is regulated and how it works.

"Inflammasome biology is attracting widespread attention from scientists and drug manufacturers because of the potential of blocking them to alleviate chronic and pathological inflammation," said Asst Prof Zhong. "As inflammation contributes to many heart diseases, targeting the inflammasome represents a new and largely untapped opportunity in heart failure research and therapeutics."

The findings were published in the *Journal of Experimental Medicine*.

More information: Rhea Nadkarni et al, Viral proteases activate the CARD8 inflammasome in the human cardiovascular system, *Journal of Experimental Medicine* (2022). DOI: 10.1084/jem.20212117

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