

Mice with missing lipid-modifying enzyme heal better after heart attack

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Credit: Martha Sexton/public domain

Two immune responses are important for recovery after a heart attack—an acute inflammatory response that attracts leukocyte immune cells to remove dead tissue, followed by a resolving response that allows healing.

Failure of the resolving response can allow a persistent, low-grade nonresolving inflammation, which can lead to progressive acute or chronic [heart failure](#). Despite medical advances, 2 to 17 percent of patients die within one year after a [heart](#) attack due to failure to resolve inflammation. More than 50 percent die within five years.

Using a mouse heart attack model, Ganesh Halade, Ph.D., and his University of Alabama at Birmingham colleagues have shown that knocking out one particular lipid-modifying enzyme, along with a short-term dietary excess of a certain lipid, can improve post-heart attack healing and clear inflammation. Halade, an assistant professor in the UAB Department of Medicine, hopes that future physicians will be able to use knowledge from studies like his to boost healing in patients after heart attacks and prevent heart failure.

"Our goal is healing, and we are reaching that goal," he said of efforts in the UAB Division of Cardiovascular Medicine.

Why are lipids and lipid-modifying enzymes important in inflammation and resolving inflammation? Three key lipid modifying enzymes in the body change the lipids into various signaling agents. Some of these signaling agents regulate the triggering of inflammation, and others promote the reparative pathway.

The lipids modified by the enzymes are two types of essential fatty acids that come from food, since mammals cannot synthesize them. One is n-6 or omega-6 fatty acids, and the other type is n-3 or [omega-3 fatty acids](#). The balance of these two types is important.

The Mediterranean diet, with a near balance of omega-3 and omega-6 fatty acids, promotes heart health. The Western diet, with large amounts of [omega-6 fatty acids](#) that greatly exceed the levels of omega-3 fatty acids, can lead to heart disease.

The three main [lipid](#)-modifying enzymes compete with each other to modify whatever fatty acids are available from the diet. So, Halade and colleagues asked, what will happen if we knock out one of the key enzymes, the 12/15 lipoxygenase?

They reasoned that this would increase the metabolites produced by the other two main enzymes, cyclooxygenase and cytochrome P450 because they no longer had to compete with 12/15 lipoxygenase for lipids to modify. This might be a benefit because those signaling lipids produced through the cyclooxygenase and cytochrome P450 pathways were already known to lead to major resolution promotion factors for post-heart attack healing.

The UAB researchers found that knocking out the 12/15 lipoxygenase and feeding the mice a short-term excess of polyunsaturated fatty acids led to increased leukocyte clearance after experimental heart attack, meaning less chronic inflammation. It also improved heart function, increased the levels of bioactive lipids during the reparative phase of healing, and led to higher levels of reparative cytokine markers. Additionally, the heart muscle showed less of the fibrosis that is a factor in heart failure.

Besides [congestive heart failure](#), persistent inflammation aggravates a vicious cycle in many cardiovascular diseases, including atherogenesis, atheroprogession, atherosclerosis and peripheral artery disease.

Halade says further mechanistic studies are warranted to develop novel targets for treatment and to find therapies that support the onset of left ventricle healing and prevent heart failure pathology.

Halade is corresponding author of the paper, "Interaction of 12/15 lipoxygenase with [fatty acids](#) alters the leukocyte kinetics leading to improved post-myocardial infarction [healing](#)," published in *Heart and*

Circulatory Physiology, a journal of the American Physiological Society.

More information: Ganesh V Halade et al, Interaction of 12/15 Lipoxygenase with Fatty Acids Alters the Leukocyte Kinetics Leading to Improved Post-myocardial Infarction Healing, *American Journal of Physiology - Heart and Circulatory Physiology* (2017). [DOI: 10.1152/ajpheart.00040.2017](https://doi.org/10.1152/ajpheart.00040.2017)

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