Research reveals blood platelets play important role in Kawasaki disease

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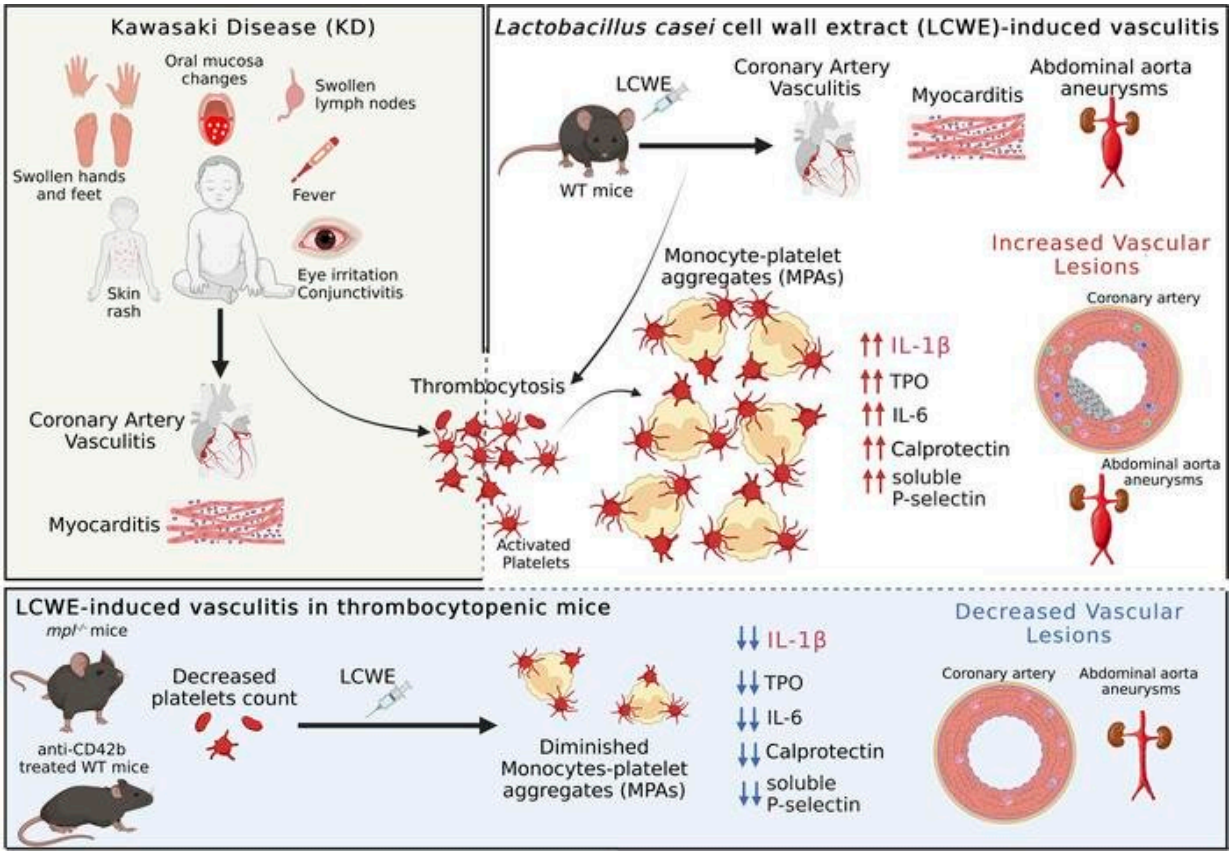

Credit: *JCI Insight* (2023). DOI: 10.1172/jci.insight.169855

Cedars-Sinai Guerin Children's investigators have advanced our understanding of the role that blood platelets play in Kawasaki disease, a serious illness that primarily affects children younger than 5 years old

and causes their blood vessels to swell.

The findings, published in *JCI Insight*, may guide the development of a new treatment for the approximately 20% of children with Kawasaki disease who aren't helped by current standard therapy. They also suggest a new biological marker clinicians can use to measure disease severity.

Without timely treatment, Kawasaki disease can damage the heart and its arteries, causing coronary artery abnormalities such as dilatation and aneurysms.

"We now have a better understanding of how this disease attacks blood vessels, which we can use to develop new therapies," said Moshe Arditi, MD, executive vice chair of the Department of Pediatrics for Research, part of Guerin Children's, and corresponding author of the study.

It was already known that children with Kawasaki disease typically develop an increased platelet count a few weeks after their first symptoms. But it was unclear until now if—and how—the platelets might contribute to cardiovascular damage.

Although rare, Kawasaki disease is the leading cause of acquired heart disease in children and adults in the U.S. The disease was first described in Japan by pediatrician Tomisaku Kawasaki in 1967.

The first symptom of Kawasaki disease is usually a sudden fever that lasts several days. The disease can also cause a rash, swelling in the hands and feet, red eyes, swollen lymph nodes and other symptoms. Scientists hypothesize that Kawasaki disease is triggered by a viral infection, but its exact cause is not yet known.

The standard treatment regimen for Kawasaki disease is an initial round of intravenous immunoglobulin (IVIG), which is meant to strengthen the

body's immune system, and high- to moderate-dose aspirin to address acute inflammation, followed by low-dose aspirin for an anti-platelet, blood-clotting effect.

In previous studies, scientists such as Arditi and colleagues reported that a group of proteins involved in the body's inflammatory response called interleukin-1 might contribute to damage in the heart and blood vessels of children with Kawasaki disease.

Arditi and colleagues reported that two inflammatory molecules, IL-1α and IL-1β, which signal through the interleukin-1 receptor, induce heart damage and aneurysm formation in laboratory mice with a Kawasaki-like illness. They also have discovered that treatments that work against IL-1 molecules or against the interleukin-1 receptor may prevent coronary artery lesion formation. Their work has led to clinical trials involving a treatment called anakinra, which suppresses and blocks the function of the interleukin-1 receptor.

In their latest study, investigators describe the interactions between platelets and monocytes, which are a type of white blood cell. The three classes of cells that circulate in blood are white blood cells, red blood cells and platelets.

To reach these findings, Arditi and colleagues analyzed blood samples from children with Kawasaki disease and discovered the genes involved in the activation of platelets are overexpressed more frequently during intense phases of the disease.

The investigators also studied laboratory mice with Kawasaki-like inflamed blood vessels and noted increased platelet counts. In addition, they observed the formation of monocyte-platelet aggregates (MPAs), which occur when platelets bind to monocytes. Platelets and MPAs are known to increase production of interleukin-1.

"It is likely MPAs amplify the production of IL-1βs and thus stimulate inflammation that causes vascular damage," said Magali Noval Rivas, Ph.D., associate director of the Infectious and Immunological Diseases Research Center and assistant professor of Pediatrics and Biomedical Sciences at Cedars-Sinai, and another senior author of the study.

Investigators observed that laboratory mice with a Kawasaki-like illness and a higher number of MPAs also had increased IL-1β formations and were more likely to have vascular lesions. When the investigators used certain drugs to deplete the platelets in mice, which led to less MPA formation, the severity of the blood vessel inflammation and lesions decreased.

"These findings support a strategy involving therapy to block MPA formation, especially in children whose bodies don't respond to IVIG, and at the end emphasizes the importance of anti-IL-1 therapies in Kawasaki disease patients," said Arditi, who is also the GUESS?/Fashion Industries Guild Chair in Community Child Health and leads the Infectious and Immunologic Diseases Research Center at Cedars-Sinai. "MPAs could also serve as a potential marker of disease severity that could help with tailoring the intensity of treatments."

Other Cedars-Sinai investigators involved in the study include Youngho Lee, Ph.D.; Nobuyuki Nosaka, MD, Ph.D.; Masanori Abe, MD, Ph.D.; Daisy Martinon; Malcolm Lane; Debbie Moreira; Shuang Chen, MD, Ph.D.; and Rebecca A. Porritt, Ph.D.

"This study and others from Arditi and colleagues are laying the groundwork for a significantly different treatment landscape for children with Kawasaki disease," said Ophir Klein, MD, Ph.D., executive director of Cedars-Sinai Guerin Children's and the David and Meredith Kaplan Distinguished Chair in Children's Health.

Arditi and colleagues continue to study the processes involved in the development of cardiovascular lesions in Kawasaki disease and potential ways to block MPAs and IL-1 pathways.

More information: Begüm Kocatürk et al, Platelets exacerbate cardiovascular inflammation in a murine model of Kawasaki disease vasculitis, *JCI Insight* (2023). DOI: 10.1172/jci.insight.169855

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