New findings reveal how recovery progresses following inflammation triggered by injury or illness

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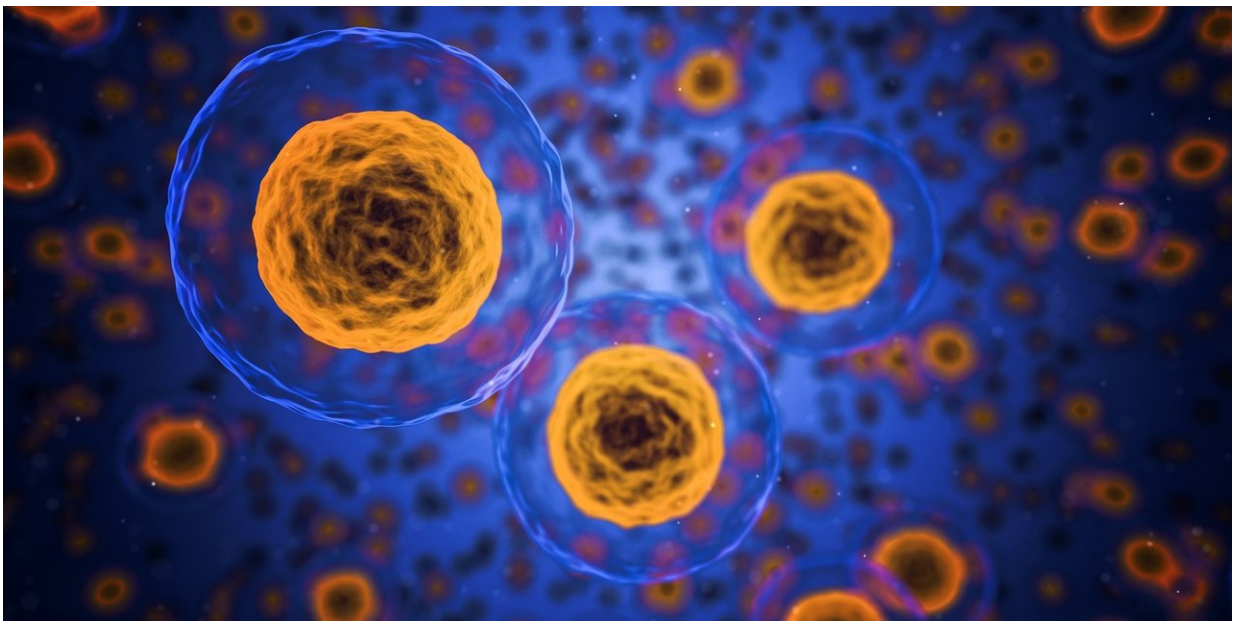

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Inflammation is the body's first line of defense, occurring as droves of immune cells rush to the site of injury or acute illness to make repairs and stem further damage.

When successful, inflammation helps the body survive and heal after trauma. However, when the recovery following an inflammatory

response goes awry, it signals that damage is still occurring—and the inflammation itself can cause further injury, leading to more-severe illness or even death.

But what differentiates a good inflammatory recovery from a bad one?

A new study, led by researchers at Harvard Medical School and Massachusetts General Hospital, published August 22 in *Nature Communications*, yields critical clues.

The scientists identified universal features of the inflammatory responses of patients who successfully recovered after surgery or acute illnesses such as COVID-19, heart attack, and sepsis. These features, they discovered, include precise paths that white blood cell and platelet counts follow as they return to normal.

If reaffirmed in further studies and eventually codified as a clinical guideline, the findings could help clinicians more quickly recognize when an individual patient's recovery isn't going well, allowing them to intervene earlier.

An ancient process

Inflammation is a generic response to almost all diseases— and, as such, people have been attempting to describe it for thousands of years. In ancient Rome, medical writer Aulus Celsus outlined the four cardinal symptoms of inflammation: redness, warmth, swelling, and pain—and later, physician and surgeon Galen added loss of function to the list. Today, scientists know that the symptoms of inflammation arise as the immune system mounts a response to injury or acute illness, sending out protective white blood cells, proteins, and chemical factors that cause physiological changes in the body.

Although clinicians today are good at identifying patients who are experiencing inflammation based on signs like high white blood cell count or fever, "there's no guidance on assessing how the inflammation is going, and whether it's subsiding in an appropriate manner," said senior author John Higgins, professor of systems biology in the Blavatnik Institute at HMS. "As physicians, we are surprisingly ill-equipped to distinguish patients whose inflammatory response is going well from patients whose response is not."

Yet knowing whether inflammation is effectively responding to the illness and progressing toward recovery is essential, since it can help doctors decide whether to stand back and let a patient's body heal on its own or intervene.

Higgins and his team set out to understand inflammatory recovery to determine whether there are common features to a successful recovery.

Signs of success

Because inflammation occurs in patients who are already sick, it can be a complicated process to study. Thus, the researchers knew that to isolate common features, they would need to study inflammatory recovery in a highly controlled setting.

"We needed to find a situation where everybody starts off in the same generally stable state of health, and then they all get a similar inflammatory stimulus at a specific time," explained first author Brody Foy, a research fellow in systems biology at HMS and Mass General.

They settled on nonemergency cardiovascular surgery—more specifically, coronary bypass, valve replacement, or some combination. These procedures are often performed in relatively healthy patients who have underlying heart issues but are otherwise stable and not

experiencing problems that require immediate treatment. However, all cardiovascular surgery involves considerable tissue trauma and damage as surgeons access the heart for surgical repairs, prompting a significant inflammatory response.

To identify patterns of inflammatory recovery, the researchers worked with author Thoralf Sundt, the HMS Edward D. Churchill Professor of Surgery at Mass General, to examine medical record data from 4,693 patients at Mass General who underwent cardiovascular surgery. After analyzing dozens of measurements simultaneously, they found common features in the trajectories of patients who recovered well. They homed in on two variables that reliably identified trajectories for successful inflammatory recovery: white blood cell count, which, not surprisingly, becomes elevated during inflammation, and platelet count, which decreases as platelets are used up for clotting and healing.

Among the patients who recovered well after surgery, white blood cell count decreased at a precise rate, while platelet count increased at a different, but also precise, rate. These trajectories, the researchers said, can be used to monitor recovery in a personalized way.

"Physicians usually can't track the changes in 20 different variables at once. We really wanted to be able to define good recoveries in terms of a small number of measurements that physicians and even patients are already familiar with," said author Jonathan Carlson, a hematologist and researcher at HMS and MGH.

The team then expanded the study to look at other types of surgeries that cause significant inflammation, including limb amputations, hip replacements, cesarean sections, partial colon removals, and a complex pancreas surgery called a Whipple procedure. They also looked at inflammation-causing infections such as COVID-19 and Clostridium difficile colitis, as well as sepsis, a life-threatening inflammatory

response precipitated by an infection. Finally, they analyzed patterns of recovery after events like heart attacks and strokes that cause oxygen deprivation to tissues and can prompt aberrant inflammation.

The researchers found that patients who recovered well followed the same characteristic trajectories for white blood cell count and platelet count returning to the normal range as their cardiovascular surgery counterparts—and did so no matter their condition or age. These patterns were also consistent regardless of how quickly patients recovered, or at what levels their white blood cell and platelet counts started.

Moreover, the scientists could mathematically define the precise trajectories that indicated a successful recovery: White blood cell count underwent exponential decay, whereas platelet count increased linearly after a short delay.

"What is exciting about this study is that it suggests there are common features of the recovery path for a surprisingly wide range of diseases, and if we know what a good recovery looks like, then we should be able to identify a bad one," Higgins said.

Translating results

For Higgins, these inflammatory recovery trajectories evoke the so-called Anna Karenina principle popularized by Jared Diamond in his book *Guns, Germs, and Steel*: There is only one way in which things can go right, but many ways things can go wrong. Patients who recover well generally follow a predictable pattern of decrease and increase in white blood cell count and platelet count, whereas patients who don't recover well may have counts that are either too high or too low—or simply don't change at the expected rates.

He also draws a comparison to pediatric growth charts, in which each child starts at a different point but should follow the same trajectory of growth—and thus stay in a similar percentile—for weight and height. He hopes that his team can eventually create analogous charts for inflammatory recovery to personalize healthy trajectories for individual patients with a wide range of illnesses.

Higgins and his team are working to get their findings into the hands of clinicians to help them better understand how patients are recovering from inflammation.

To illustrate this idea, Higgins highlighted the case of a 78-year-old woman admitted to the hospital after a heart attack. On day four of her recovery, her white blood cell count dropped into the normal range, suggesting that she was recovering well. However, her white blood cell count was still higher than the healthy trajectory the researchers had defined—and it proceeded to increase over the next several days, as she took a turn for the worse. In other words, the overall pattern provided a more valuable diagnostic clue than the absolute blood count number, Higgins said, by signaling a day earlier that something had gone wrong with the patient's recovery.

Higgins, however, cautions that it remains to be seen whether earlier intervention based on these harbingers of poor recovery might improve outcome. That is a subject for further research.

"Our approach really just identifies high-risk patients," Higgins said. "We still have to study whether diagnosing something a little bit earlier is actually going to help, but at least we'd have a chance to intervene."

Higgins and his team are also interested in studying the underlying biological mechanisms that cause white blood cell and platelet counts to return or fail to return to normal after injury or illness.

"These findings help generate some hypotheses for mechanisms," Higgins said. For example, it guides researchers to look at when white blood cell counts peak during inflammation, and explore the processes in the body that would lead to exponential decay after the peak.

The researchers also want to shift their focus even earlier in the process to see if they can find common features of a good response when patients initially develop inflammation after injury or illness.

"Understanding quantitatively what a good recovery looks like from the very beginning will allow us to identify at-risk patients at even earlier time points, and to design interventions that improve outcomes," said author Aaron Aguirre, HMS assistant professor of medicine at Mass General.

More information: Human Acute Inflammatory Recovery is Defined by Co-Regulatory Dynamics of White Blood Cell and Platelet Populations, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32222-2

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