Measuring immune cells before surgery may help predict recovery time, study finds

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Credit: Lynn Greyling/public domain

The behavior of a type of white blood cell can indicate how soon

patients will be back on their feet after hip surgery, according to a study by scientists at the Stanford University School of Medicine.

The scientists plan to use the findings to develop a diagnostic blood test that patients can undergo before surgery.

U.S. doctors performed more than 50 million surgeries, including some 300,000 hip surgeries, last year. While indicators for negative outcomes—like organ failure, infection and death—have been extensively studied, indicators for healthy recoveries have not.

"Some people feel great after a few days, some are in bed for a month and we don't know why," said Gabriela Fragiadakis, a graduate student in microbiology and immunology. Fragiadakis shares lead authorship of the study, which will be published online Nov. 17 in *Anesthesiology*, with Brice Gaudilliere, MD, PhD, clinical instructor of anesthesiology, perioperative and pain medicine. The senior authors are Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine, and Garry Nolan, PhD, professor of microbiology and immunology. The study will also appear in the December issue of the journal.

Focusing on monocytes

The researchers discovered that the behavior of monocytes, the largest type of white blood cells, in patients before surgery was linked to the length of their recoveries. As much as 50 percent of the variation in a patient's recovery time could be predicted based on these cells' behavior. Previously studied predictors, such as the patients' mental states or the number of immune cells at the wound site, generally account for at most 10 percent of the variation seen in patients' recovery times.

Knowing the likely recuperation times will help patients plan better for their return to work and other post-surgery commitments. For patients at

risk for longer recovery times, doctors could schedule additional physical therapy or special care, or the surgery could be postponed while exercise, dietary changes and stress-release techniques are implemented.

The work expands on research published last year on 32 patients recovering from hip-replacement surgery. These patients were relatively healthy and had complication-free surgeries. The researchers found a strong link between the speed at which these patients regained hip strength and mobility and how monocytes functioned in their blood shortly after surgery. While the cells were active in all cases, patients with supercharged monocytes took weeks longer to regain abilities such as getting out of bed, standing or walking.

Monocytes are some of the immune system's first responders. They sense the distress call from damaged cells, be it from an invading pathogen or the clean cut of a surgeon's knife. When the monocytes arrive on the scene, they go to work clearing away cellular debris and initiating wound healing. But a bigger early response of monocytes in the blood isn't necessarily better. It may disrupt the cells' ability to sense the location of the wound and slow down the healing process, said Angst.

'Surgery' in a test tube

In previous work by the researchers, the overactive monocytes and their relationship to patient recovery were measurable one hour after surgery. The next question, addressed in the current study, was whether these patterns in monocytes could be detected before a patient was wheeled into the operating room.

The researchers simulated surgery conditions in a test tube using blood they had collected from 25 of the patients in the original study an hour before the surgery. Gaudilliere likened this approach to a cardiac stress test, in which the heart is forced to work harder by having patients run

on a treadmill to uncover underlying health issues. For this "immune stress test," the researchers mixed known signaling molecules into the blood samples to trigger specific responses from the immune cellular machinery, similar to what might be set in motion during surgery.

They then analyzed the cells using mass cytometry, a technique developed in the Nolan lab that sorts and characterizes cells based on chemical tags. The tags not only precisely identify the cell types, but also reveal the internal, cell-specific processes that control the cell's behavior. Supporting their previous observations, they found that the speed at which patients regained hip function was related to the cellular processes of the monocytes.

By detecting signals from injured tissue, monocytes play a critical role in wound healing by forming new connective tissue and blood vessels. Angst suspects that when the monocytes are overly activated by surgery, their ability to migrate to the incision site is impaired.

To see if an exaggerated response by monocytes delays healing, Angst and Gaudilliere are now using imaging technology to observe the cells in the wounds of patients undergoing surgery, as well as in wounds of mice who undergo a surgery that is similar to the hip replacement studied in patients.

Replicating, refining and broadening the findings

Dan Sessler, MD, professor and chair of outcome research at the Cleveland Clinic, who was not involved with the study, sees great value in adapting the paper's results into a test. Predicting a patient's recovery is "clinically important, and we don't do a good job," he said.

In a new Stanford study with a larger cohort—about 80 hip-replacement patients—Angst and Gaudilliere are hoping to refine the initial study's

findings. They will assign more of the mass cytometer's chemical tags to the cellular machinery of the monocytes, allowing them to closely study the cells' internal processes and increase their understanding of cellular events that best predict recovery after surgery.

"The first study was exploratory," said Angst. "We are now in the position to ask specific questions and prospectively validate our findings." If his team can pinpoint the most critical activated proteins, they can develop a simpler assay. Most hospital labs already have cell analysis machines that could readily measure activity of the monocytes. "Once we know what we're testing for, we can use simpler methods using machines already in the hospital, and it can be done in a couple of hours," said Fragiadakis.

The development of a surgery-recovery prediction test is an example of Stanford Medicine's focus on precision health, which aims to enable researchers and physicians to better predict individual risks for specific diseases, develop approaches to early detection and prevention, and help clinicians make real-time decisions about the best way to care for patients.

Provided by Stanford University Medical Center

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