Platelets modulate clotting behavior by 'feeling' their surroundings

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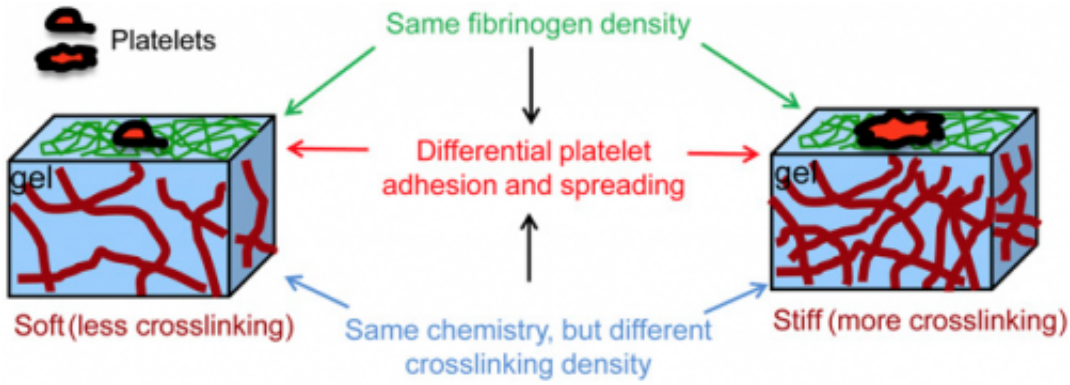

Researchers devised a way to separate the physical stiffness of the material where platelets spread out from its biochemical properties. Credit: Wilbur Lam

Platelets, the tiny cell fragments whose job it is to stop bleeding, are very simple. They don't have a cell nucleus. But they can "feel" the physical environment around them, researchers at Emory and Georgia Tech have discovered.

Platelets respond to surfaces with greater stiffness by increasing their stickiness, the degree to which they "turn on" other platelets and other components of the clotting system, the researchers found.

"Platelets are smarter than we give them credit for, in that they are able to sense the physical characteristics of their environment and respond in a graduated way," says Wilbur Lam, MD, PhD, assistant professor in the

Department of Pediatrics at Emory University School of Medicine and in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

The results are published in *Proceedings of the National Academy of Sciences*. The first author of the paper is research associate Yongzhi Qiu. Lam is also a physician in the Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta.

The researchers' findings could influence the design of medical devices, because when platelets grab onto the surfaces of catheters and medical implants, they tend to form clots, a major problem for patient care.

Modifying the stiffness of materials used in these devices could reduce clot formation, the authors suggest. The results could also guide the refinement of blood thinning drugs, which are prescribed to millions to reduce the risk of heart attack or stroke.

The team was able to separate physical and biochemical effects on platelet behavior by forming polymer gels with different degrees of stiffness, and then overlaying them each with the same coating of fibrinogen, a sticky protein critical for blood clotting. Fibrinogen is the precursor for fibrin, which forms a mesh of insoluble strands in a blood clot.

With stiffer gels, platelets spread out more and become more activated. This behavior is most pronounced when the concentration of fibrinogen is relatively low, the researchers found.

"This variability helps to explain platelet behavior in the 3D context of a clot in the body, which can be quite heterogenous in makeup," Lam says.

Qiu and colleagues were also able to dissect platelet biochemistry by

allowing the platelets to adhere and then spread on the various gels under the influence of drugs that interfere with different biochemical steps.

Proteins called integrins, which engage the fibrinogen, and the protein Rac1 are involved in the initial mechanical sensing during adhesion, while myosin and actin, components of the cytoskeleton, are responsible for platelet spreading.

"We found that the initial adhesion and later spreading are separable, because different biochemical pathways are involved in each step," Lam says. "Our data show that mechanosensing can occur and plays important roles even when the cellular structural building blocks are fairly basic, even when the nucleus is absent."

More information: Platelet mechanosensing of substrate stiffness during clot formation mediates adhesion, spreading, and activation, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1322917111

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