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Microfluidics

Blood-Clotting Model

Simple chemical system provides insights into complex biological phenomenon

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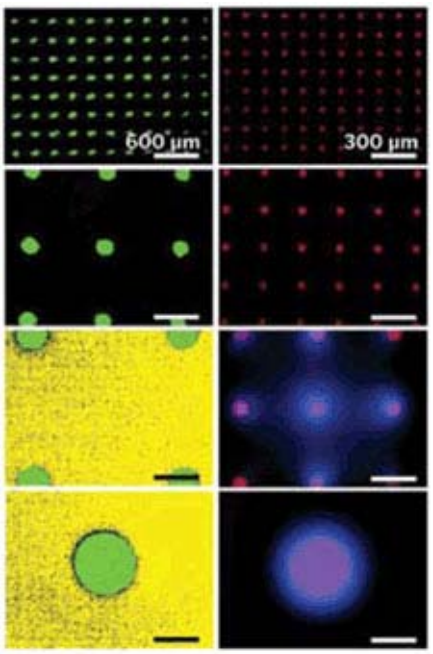
A simple chemical system could help researchers understand the complex biological system governing blood clotting.

Chemistry professor Rustem F. Ismagilov and graduate students Christian J. Kastrup, Matthew K. Runyon and Feng Shen at the University of Chicago use a modular chemical system to mimic initiation of blood clotting in the complex biological system of hemostasis, which comprises about 80 reactions (*Proc. Natl. Acad. Sci. USA* **2006,** *103,* 15747).



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Trigger In both the chemical model (left) and human blood plasma (right), clotting happens only when the activator patches reach a certain threshold size, 400 µm in the chemical system and 100 µm in plasma. Green = chemical activator, yellow = gelled alginic acid, red = biological activator, purple = blood clot.

"The clotting network is just too complex to model the reactions and transport and get some sort of intuitive understanding," Ismagilov says. "The problem with simplifying the network is that everything is important. You can't just study it one reaction at a time."

To get around this problem, the Chicago researchers looked at the big picture and broke the network into three modules that describe the kinetics of the overall phenomenon. These modules demonstrate autocatalytic production of clotting activators, depletion of those activators by diffusion, and formation of a clot at high concentrations of activators. In their model system, catalytically generated acid initiates the gelling of alginic acid, much as tissue factor protein initiates clotting of blood.

The researchers performed the experiments in microfluidic devices, one for the chemical system and one for blood plasma. "Microfluidics allows us to localize the components," Ismagilov says.

Key to Ismagilov's chemical model are patches containing clotting activators generated on the surface of the microfluidic channels. The model predicts that clotting will not occur when the patches of activator are below a threshold size. By using the chemical model, the team could predict the threshold size of patches required for clotting of blood plasma. The initiation of the clotting depends on the size of individual patches rather than the sum of all the patches. Subthreshold patches initiate clotting only if they are clustered densely enough to behave as a single patch.

"There is a lot of literature right now where people argue about whether certain concentrations of tissue factor can or cannot initiate clotting," Ismagilov says. "The point we're making is that knowing the average concentration isn't enough. You actually have to know the localization of tissue factor."

In an accompanying commentary, Irving R. Epstein of Brandeis University writes: "This tour de force significantly extends the scope of chemical reactions as a source of fruitful models for complex biological processes."

Ismagilov wants to move to more medically relevant applications. "We need to push these results into model organisms and then into people," he says, "because that's where these results will make the most impact" in understanding wound healing and clotting diseases such as deep vein thrombosis.

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