Blood's clotting cells harbor 'ticking time bombs'

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Fragments of cells in the blood known as platelets—which form blood clots and assist in wound healing—have internal “clocks” that act like ticking time bombs, predetermining their death from the moment they are born, according to a new study in the March 23 issue of the journal *Cell*, published by Cell Press.

The researchers said that the findings could have “profound implications” for the diagnosis and treatment of platelet disorders. Perhaps even more importantly, they said the discovery suggests that chemical treatments that effectively set those clocks back might increase the shelf life of donated blood platelets, which expire after just five days under the storage conditions now required.

The researchers discovered that platelets’ characteristically short life span, which for humans is 10 days, is set by the amount of a prosurvival protein they contain. As that protein dwindles, its cellular “nemesis” takes over, causing the specialized clotting cells to commit a programmed form of suicide called apoptosis.

“We found that platelets undergo really classical apoptosis,” said David Huang of The Walter and Eliza Hall Institute of Medical Research in Australia. “It’s surprising in many ways because platelets are an unusual cell type that lacks a nucleus. We didn’t know what was controlling their life span.” Cell nuclei contain the genetic instructions that ultimately direct the activities of other kinds of cells.

“The finding has a whole list of potential implications,” added study collaborator Benjamin Kile, also of The Walter and Eliza Hall Institute of Medical Research. “For us, probably the most important is the possibility for extending platelet life span in blood banks.” Such an extension might be achieved by increasing levels of the prosurvival protein, called Bcl-xL, or by blocking its rival death protein, Bak.

“If the platelet storage time could be extended from five to eight or 10 days, it would make a lot of difference for clinical and blood banking practice,” Huang said.

In the United States alone, approximately 12 million units of platelets are transfused each year, primarily in patients undergoing treatment for cancer, the researchers said. Patients who are administered chemotherapy drugs often require platelet support to reduce their risk of bleeding. That’s because the constituents of bone marrow that produce the clotting cells are “severely affected” by the cancer-fighting agents, Huang explained.

For reasons that aren’t yet entirely clear, donated platelets must be stored at room temperatures, the researchers said. When kept under colder conditions, transfused platelets are recognized as foreign by a recipient’s immune system and quickly cleared from the bloodstream.

“The problem at room temperature is that biological processes occur quickly, leading to a rapid decline in viability,” Kile said. That decline, in addition to problems with bacterial contamination, has precluded platelet’s storage for more than five days.

In search of genes that influence platelet number in the current study, the researchers first screened mice exposed to a mutagenic chemical for low platelet counts. Their search uncovered two such mouse strains, each bearing different mutations in Bcl-xL. Mice specifically engineered to

lack Bcl-xL also were deficient in platelets, they showed.

“It was an unexpected result, and the seed for the whole story,” Kile said of the initial discovery.

The researchers at first suspected the problem in the Bcl-xL-deficient animals might stem from a defect in the production of platelets in the bone marrow. When that theory failed to pan out, they were initially “left scratching their heads,” Kile said.

They then realized that Bcl-xL might serve to keep platelets alive, just as it does in other cells. Indeed, they found evidence in mice that prosurvival Bcl-xL constrains the activity of suicide-inducing Bak to maintain platelet survival. As Bcl-xL degrades, older platelets are primed for cell death.

Genetic or drug treatments that blocked Bcl-xL reduced platelets’ life span and caused mice to become platelet deficient, they found. Eliminating Bak corrected those defects, and platelets from Bak-deficient mice lived longer than normal, they reported.

The drug used by the researchers was a “BH3 mimetic,” a class of anticancer therapy that is now under development, Huang explained. The drugs work by targeting Bcl-xL and related prosurvival genes in tumor cells.

Bcl-xL’s newfound role reveals that the new cancer drugs will likely lead to a decline in platelet numbers. However, the researchers added, “the side effect is likely to be self-limiting as normal bone marrow has the capacity to compensate by increased platelet production.”

In addition to the new platelet discovery’s possible practical applications, the findings also have intriguing biological implications.

“It suggests at the molecular level that cells are really programmed to die by default within a given period of time unless another signal overrides it,” Huang said.

“All cells may have such a clock,” he continued. “However, in most cells that clock may be rewired and modified by the manufacture of proteins. Their clocks could, in essence, be rewound.”

In contrast, he said platelets’ lack of a nucleus leaves them without a mechanism for turning back the clock. It will be interesting to see if a similar clock fixes the life span of red blood cells—the oxygen carriers of the bloodstream—which also lack a nucleus, the researchers said.

Source: Cell Press