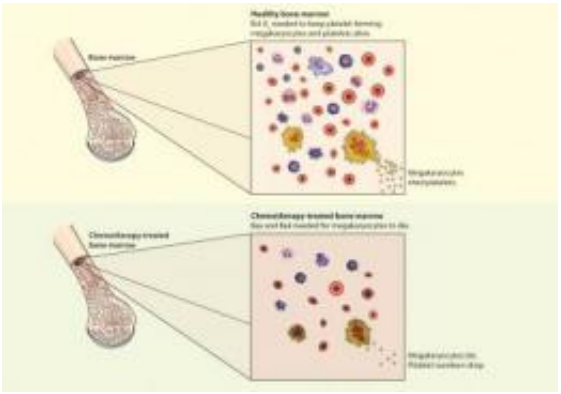
Discovery helps explain why chemo causes drop in platelet numbers

25 September 2011



Healthy bone marrow (top) contains many cell types including platelet-producing megakaryocytes (brown). The pro-survival protein Bcl-xL is important for keeping megakaryocytes alive. After chemotherapy (below) many cell types in the bone marrow, including megakaryocytes, are killed through a process requiring the pro-death proteins Bax and Bak. Platelet numbers can be depleted in the blood by chemotherapy because of its toxicity for both platelets and megakaryocytes. Credit: Walter and Eliza Hall Institute of Medical Research

Scientists at the Walter and Eliza Hall Institute have identified a way that chemotherapy causes platelet numbers to drop, answering in the process a decade-old question about the formation of platelets, tiny cells that allow blood to clot.

Platelets are formed by a process called 'shedding' where small fragments break off megakaryocytes (large cells normally found in the bone marrow).

Drs Emma Josefsson, Chloé James and Benjamin Kile from the institute's Molecular Medicine and Cancer and Haematology divisions have been investigating how the survival of platelet- forming megakaryocytes is controlled at a molecular level.

The life-or-death decisions of cells are controlled by the Bcl-2 family of proteins. Some 'pro-death' Bcl-2 family proteins cause cells to die, while an opposing 'pro-survival' faction prevents cell death, allowing cells to survive.

In the past decade it has been thought that platelets are formed by megakaryocytes through a process similar to cell death, Dr Josefsson said. "Our research tested this assumption by examining the molecules that are required for programmed cell death. We found that, at a molecular level, platelet formation does not occur by a death-like process.

"We found that pro-death Bcl-2 family proteins were not required for platelet formation from megakaryocytes," Dr Josefsson said. "In fact, pro-survival Bcl-2 family proteins are essential for keeping megakaryocytes alive so they can make platelets."

Low platelet numbers are a side-effect of chemotherapy and, whilst this has long been ascribed to the death of megakaryocytes and their precursors, the mechanisms responsible have remained unclear. The research team showed that chemotherapy kills megakaryocytes by its action on Bcl-2 family proteins, Dr Josefsson said. "Our work has shown that chemotherapy activates 'pro-death' Bcl-2 proteins to kill megakaryocytes, meaning patients are less capable of producing platelets as they recover from cancer treatment." The research was published today in the *Journal of Experimental Medicine*.

Institute scientist Professor Don Metcalf has researched blood formation for the past 50 years and was part of the research team. "For the past decade many researchers around the world have been wondering what role Bcl-2-family proteins play in platelet formation," he said. "This study is important for resolving a longstanding debate about platelet formation, and in the long term may lead to new strategies to prevent chemotherapy-induced thrombocytopenia (a deficiency in platelets)."

Provided by Walter and Eliza Hall Institute

APA citation: Discovery helps explain why chemo causes drop in platelet numbers (2011, September 25) retrieved 5 November 2022 from https://medicalxpress.com/news/2011-09-discovery-chemo-platelet.html

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