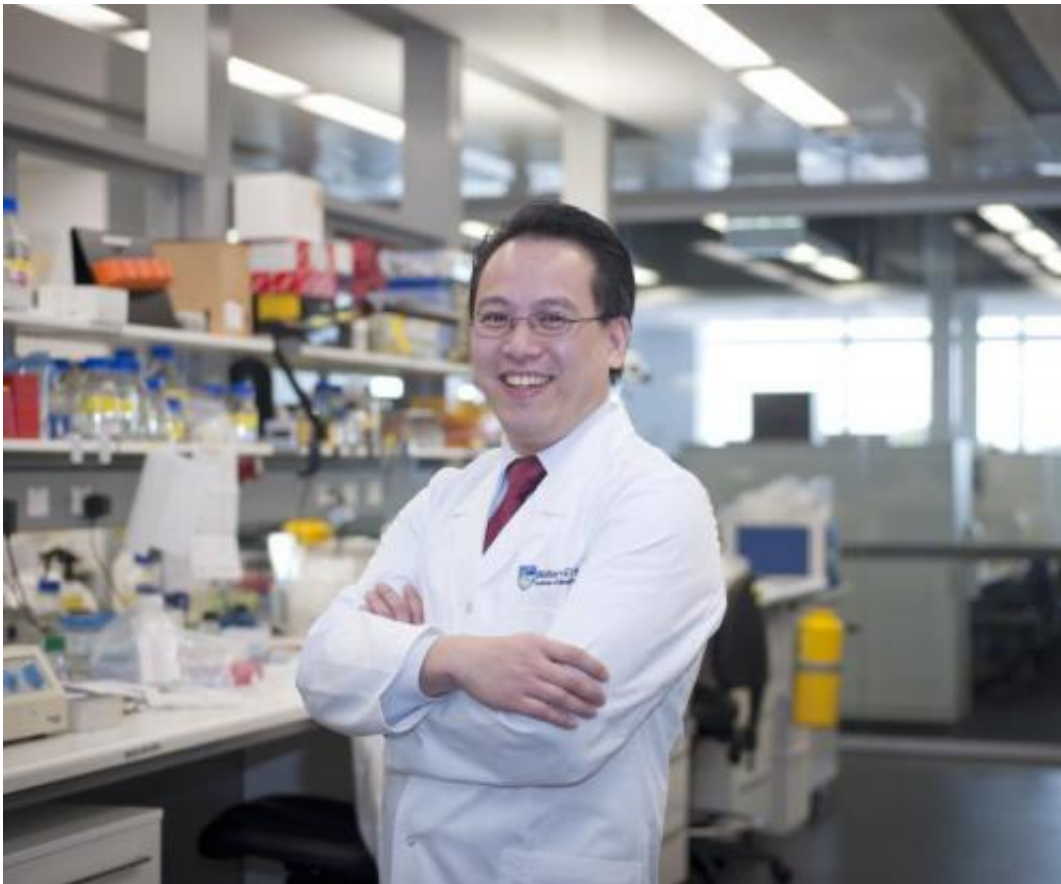


Solution to platelet 'puzzle' uncovers blood disorder link

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Dr. Ashley Ng and colleagues from the Walter and Eliza Hall Institute in Melbourne, Australia, have solved a puzzle about how blood-making hormones stimulate the bone marrow to make platelets. Credit: Walter and Eliza Hall Institute of Medical Research

Melbourne researchers have solved a puzzle as to how an essential blood-making hormone stimulates production of the blood clotting cells known as platelets.

Platelets are essential for stopping bleeding and are produced by small fragments breaking off their 'parent' cells, called megakaryocytes.

The discovery, made by scientists at the Walter and Eliza Hall Institute, identified how [bone marrow](#) cells could become overstimulated and produce too many [platelets](#). In blood diseases such as essential thrombocythemia, too many platelets can lead to clogging of the blood vessels, causing clots, heart attack or strokes.

Institute researchers Dr Ashley Ng, Dr Maria Kauppi, Professor Warren Alexander, Professor Don Metcalf and colleagues led the research, published today in the journal *Proceedings of the National Academy of Sciences*.

Dr Ng said the hormone thrombopoietin was responsible for signalling [bone marrow cells](#) to produce platelets but, until now, researchers did not know precisely which cells responded to its signals. By studying the receptor for thrombopoietin, called Mpl, on [blood cells](#) in the bone marrow, the team pinpointed the cells involved in making platelets after thrombopoietin stimulation, and made an unexpected discovery.

"Thrombopoietin did not directly stimulate the platelet's 'parent' cells, the megakaryocytes, to make more platelets," Dr Ng said.

"Thrombopoietin signals actually acted on stem cells and progenitor cells, several generations back."

To reach this conclusion, the researchers genetically removed the Mpl receptors from megakaryocytes and platelets. Dr Ng said the result was very surprising. "The progenitor and [stem cells](#) in the bone marrow

began massively expanding and effectively turned the bone marrow into a megakaryocyte-making machine," Dr Ng said.

"Our findings support a theory whereby megakaryocytes and platelets control platelet numbers by 'mopping up' excess amounts of thrombopoietin in the bone marrow. In fact, we show this 'mopping up' action is absolutely essential in preventing blood disease where too many megakaryocytes and platelets are produced."

The findings may have implications for human disease, Dr Ng said. "We know people with myeloproliferative disorders, such as essential thrombocythemia, produce too many megakaryocytes and platelets," he said.

"Interestingly, previous studies have shown megakaryocytes and platelets in people with essential thrombocythemia have fewer Mpl receptors, which fits our model for excessive [platelet production](#). By using genetic 'signatures', we were able to compare the blood progenitor cells responsible for overproducing [megakaryocytes](#) in our model, to progenitor cells in people with essential thrombocythemia. We were able to show that [progenitor cells](#) in our model and in patients with essential thrombocythemia, had a signature of excessive thrombopoietin stimulation.

"We think this study now provides a comprehensive model of how thrombopoietin controls platelet production, and perhaps gives some insight into the biology and mechanism behind specific myeloproliferative disorders," Dr Ng said.

More information: Mpl expression on megakaryocytes and platelets is dispensable for thrombopoiesis but essential to prevent myeloproliferation, *PNAS*,
www.pnas.org/cgi/doi/10.1073/pnas.1404354111

Provided by Walter and Eliza Hall Institute

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