What the Goldilocks gene means for blood-based cancers

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Assistant Professor Leonardo Salmena (centre) with his graduate students (l to r) Mark Sharobim, Meong Hi Son, Irakli Dzneladze, John Woolley and Martino Babra. Credit: Erin Howe

INPP4B is the Goldilocks of genes.

If there is too little of it, you're at a greater risk for developing a variety of cancers. And new research at the University of Toronto has discovered that, if there's too much, you're also at a greater risk of

developing leukemia – and it's harder to treat because you're also more resistant to chemotherapy.

INPP4B stands for Inositol polyphosphate-4-phosphatase, type II. It's a protein in your cells that was thought to put the brakes on the development of tumours. When it's "just right" – which in this case means it's not over-expressed in acute myeloid leukemia (AML) – you are likely to have a less aggressive and more treatable disease.

"We've known for a while now that when INPP4B is under-expressed in breast and other cancers, the disease is more aggressive" explains Leonardo Salmena, an assistant professor in the department of pharmacology and toxicology and affiliate scientist at the Princess Margaret Cancer Centre. "It means that tumour growth happens faster, which also makes it more difficult to treat."

The researchers behind that discovery included Salmena and was led by Professor Lewis Cantley of Weill Cornell Medical College and New York Presbyterian Hospital, who was named a recipient of the Canada Gairdner International Award last week.

When Salmena and PhD candidate Irakli Dzneladze began exploring INPP4B in blood-based cancers like AML, they expected to find a similar pattern. Instead, they found the opposite. Their results were published in the journal *Leukemia*.

"We didn't find any association between the under-expression of INPP4B and disease outcome," says Salmena. "Instead, we found that over-expression of INPP4B was associated with more aggressive AML."

The research team, which included Dr. Mark Minden, used clinical data drawn from the Princess Margaret Cancer Centre and The Cancer Genome Atlas. They found that INPP4B was reliable a biomarker that

can help doctors predict your outcome. When too much INPP4B was found, the risk of death for AML patients increased two-fold.

They also found that too much INPP4B made patients resistant to common treatments for leukemia, like chemotherapy or gamma radiation. To work, these treatments have to be able to damage the DNA of cancer cells. INPP4B, however, strengthens cells – including cancer cells – making it harder for these treatments to be effective.

Salmena and his team are now trying to understand what causes the over-expression of INPP4B in leukemia.

"We now know that INPP4B is an important part of the leukemia puzzle. The question now is how can we control it. Targeting proteins like INPP4B has proven very difficult in the past, but now that we've identified a new pathway in cancer, we can potentially develop new ways to get at it," says Salmena.

More information: "Evidence that Inositol Polyphosphate 4-Phosphatase Type II Is a Tumor Suppressor that Inhibits PI3K Signaling." DOI: dx.doi.org/10.1016/j.ccr.2009.06.006

"INPP4B overexpression is associated with poor clinical outcome and therapy resistance in acute myeloid leukemia." *Leukemia* accepted article preview 4 March 2015; DOI: 10.1038/leu.2015.51

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