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How molecules out of balance lead to human multiple myeloma and other cancers

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An international team of scientists has identified processes that are heavily implicated in human multiple myeloma and other B cell cancers, moving us closer to developing quick tests and readouts that could help in the tailored treatment of patients.

B cells, the white blood cells that produce antibodies, form a key part of our 'immune response'. To remain healthy, we need to maintain the right number of B cells, not too many and not too few. This in turn relies on an intricate interplay of molecules within our bodies, and inside our B cells.

Professor Fabienne Mackay, Professor Klaus Rajewsky and Dr Marc Schmidt-Supprian, from Sydney's Garvan Institute of Medical Research, Harvard Medical School and Germany's Max Planck Institute of Biochemistry respectively, have identified two processes that appear to influence B cell driven cancers. Their findings are published online this week in the international journal *Proceedings of the National Academy of Sciences*.

"We already know that the over-expression or mutation of molecules known as NIK and TRAF3 in B cells is associated with human multiple myeloma," said Professor Mackay. "Our collaborative research uncovered two distinct processes involving these molecules that help explain why."

The first process involves NIK, an enzyme that acts closely with BAFF,

the substance that regulates the number of B cells in our bodies. Work done previously by Professor Mackay on BAFF showed that levels correlate with B cell hyperplasia (expansion) and cancer. The current study shows that if we have too much NIK in our systems, then our B cells will also expand, and we will be prone to cancer.

The second process, associated with the first, involves TRAF3, the molecule that negatively regulates NIK.

Professor Mackay explained that in a healthy person, NIK and TRAF3 work together, helping to maintain the right number of B cells for survival. "But when there are mutations in either molecule, they become uncoupled. In other words, TRAF 3 no longer represses the action of NIK when necessary."

"The important thing to note is that when you uncouple NIK from TRAF3 action, its levels are not necessarily going to go up, but its function is going to be changed. This can lead to B cell hyperplasia and cancer."

"Our paper is saying 'be careful'! Sometimes you can find a patient without high expression of NIK, so you think NIK is not implicated, where it might be."

"In the very near future, we will have the capacity to do blood tests and test for specific gene mutations in patients. Once you identify a mutation, you can bypass the action of that gene, with targeted medications."

"Both NIK and TRAF3 are molecules, so can potentially be targeted by pharmaceuticals. We anticipate that new treatments for cancers may emerge from our findings."

Source: Research Australia