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Drug that 'switches off' faulty gene in cancer cells could reverse treatment resistance

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New insights into a gene linked to the development of blood cancers could help to explain why some patients are resistant to a common drug used in cancer treatment.

Scientists at the University of Glasgow showed that abnormal activity of a gene called RUNX1 interferes with signalling molecules, causing cancer cells to become resistant to steroids. The findings suggest that drugs that can switch off the gene may be able to reverse this resistance in patients.

The study, which was funded by the charities Bloodwise and Cancer Research UK, is published in the *Journal of Cellular Biochemistry*.

The RUNX family of genes help maintain healthy blood cell formation by regulating the activity of other genes involved in the process. Abnormal functioning of one of the genes—called RUNX1—is known to play a critical role in allowing many types of leukaemia and lymphoma to develop.

The team, led by Professors James Neil and Dr Anna Kilbey, studied human lymphoma cells and mice with lymphoma in the laboratory to determine the role that RUNX1 plays in cancer development.

They found that RUNX1 either suppresses or promotes the growth of cancer depending on how the gene is switched on or off, or 'expressed'. The gene was able to alter the balance of sphingolipids – 'signalling' lipid

molecules found in the cell membrane that regulate programmed cell death.

When RUNX1 was abnormally expressed, the production of sphingosine-1-phosphate, a lipid that stimulates cell growth and survival, was greatly enhanced and levels of ceramides, which promote cell death, were reduced. The findings help to explain why patients can become resistant to dexamethasone, a steroid drug used in cancer treatment that works by inducing sphingolipids in lymphoma cells to promote cell death.

James Neil, Professor of Molecular and Cellular Oncology at the Institute of Infection, Immunity and Inflammation, said: "Abnormal RUNX1 expression made lymphoma cells more resistant to treatment with dexamethasone, suggesting that drugs that can switch off the gene may be able to reverse treatment resistance in patients. An exciting possibility would be to see if new RUNX1-inhibiting drugs could be used in combination with steroids to reduce treatment resistance – something that we are looking forward to testing in the lab."

Dr Alasdair Rankin, Director of Research at Bloodwise, said: "Steroids such as dexamethasone are a key component of combination treatments for many types of leukaemia and lymphoma. Although resistance to dexamethasone is common, the underlying mechanisms have so far been poorly understood. This new research not only sheds more light on how the RUNX genes enable cancer to develop if they go wrong, but could also have a direct influence on the development of new drug combinations to prevent resistance to steroids."

Anna Perman, Cancer Research UK's senior science information manager, said: "Some patients' cancers become resistant to treatment, and understanding how this can happen is vital to improving survival. This early research, carried out in lymphoma cells, has identified how

faulty RUNX1 can contribute to resistance to steroid treatment. The next steps will be to see if targeting RUNX1 could help prevent cancer cells becoming resistant to steroid treatment, before drugs can be developed to help patients."

More information: A. Kilbey et al. Runx1 Orchestrates Sphingolipid Metabolism and Glucocorticoid Resistance in Lymphomagenesis, *Journal of Cellular Biochemistry* (2017). DOI: 10.1002/jcb.25802

Provided by Bloodwise