Protein 'handbrake' halts leukaemia in its tracks

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Researchers from the Walter and Eliza Hall Institute in Melbourne, Australia, have shown they can stop leukaemia in its tracks by targeting a protein that puts the handbrake on cancer cell growth.The researchers discovered that targeting a protein called Hhex could cure acute myeloid leukaemia (AML) in preclinical disease models, and could be a key target for new therapies for human leukaemia. Credit: Walter and Eliza Hall Institute

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The researchers discovered that targeting a protein called Hhex could cure acute myeloid leukaemia (AML) in preclinical disease models, and could be a key target for new therapies for human leukaemia.

Dr Ben Shields and Dr Matt McCormack from the Walter and Eliza Hall Institute discovered that loss of the Hhex protein put the handbrake on leukaemia cell growth and division. The protein is a critical factor enabling AML cells to grow uncontrollably, a hallmark of cancer.

AML is an aggressive blood cancer that appears suddenly, grows quickly and has a poor prognosis. Existing treatments for AML are associated with serious side-effects. About three quarters of patients relapse after only a short period of treatment, with a five-year survival rate of just 24 per cent.

Dr McCormack said discovering how AML overcame normal cellular controls on growth and division was a breakthrough in the search for new therapies.

"There is an urgent need for new therapies to treat AML," said Dr McCormack. "We showed blocking the Hhex protein could put the brakes on leukaemia growth and completely eliminate AML in preclinical models. This could be targeted by new drugs to treat AML in humans."

He said Hhex was a particularly attractive therapeutic target because it was overproduced in leukaemia and, while essential for leukaemia cell growth, was not needed by healthy blood cells.

"Most existing treatments for AML are not cancer cell-specific, and unfortunately kill off healthy cells in the process," Dr McCormack said.

"Hhex is only essential for the leukaemic cells, meaning we could target and treat leukaemia without toxic effects on normal cells, avoiding many of the serious side-effects that come with standard cancer treatments. We also know that most people with AML have increased levels of Hhex, often associated with adverse outcomes, further indicating it is an important target for new AML drugs."

Dr Shields said AML cells switched off the controls that strictly manage cell growth and division. "Every cell has control genes that are activated when a cell is stressed, such as in the early stages of cancer, and stop the damaged cell from reproducing." Dr Shields said.

While these control genes are still present in AML cells, they are switched off through a process called epigenetic modification. "Hhex works by recruiting epigenetic factors to growth control genes, effectively silencing them. This allows the leukaemia cells to reproduce and accumulate more damage, contributing to the speed of AML progression," Dr Shields said.

Dr McCormack said drugs that inhibit epigenetic modification had been previously used to treat AML, but caused significant toxicity because their targets were also required for normal blood cell function.

"Unlike the epigenetic factors targeted previously, Hhex only regulates a small number of genes and is dispensable for normal blood cells. This gives us a rare opportunity to kill AML cells without causing many side effects," said Dr McCormack. "We now hope to identify the critical regions of the Hhex protein that enable it to function, which will allow us to design much-needed new drugs to treat AML."

The research was published today in the journal *Genes & Development*.

More information: Benjamin J. Shields et al. Acute myeloid leukemia requires Hhex to enable PRC2-mediated epigenetic repression of , *Genes & Development* (2016). DOI: 10.1101/gad.268425.115

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