Targeting leukemia cell's gene 'addiction' presents new strategy for treatment

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An international team of scientists studying acute forms of Leukaemia have identified a new drug target to inhibit the genes which are vital for the growth of diseased cells. The research, reported in *EMBO Molecular Medicine*, reveals how leukaemia cells become 'addicted' to genes, which if targeted could prevent diseased cells from developing.

The team, led by Dr Veronika Sexl from the University of Vienna, carried out their research on acute lymphoid leukaemia (ALL) and chronic myelogenous leukaemia (CML), which can both be caused by fusion protein, Bcr-Abl, created through the joining of two or more genes originally coded for separate proteins.

This joining of genes results in a complex tumor supporting 'network' which supports the growth and survival of the leukaemic cells. Inhibitor drugs such as 'Imatinib' can block vital signals and lead to leukemia cell death, but there are several mutations which can resist these inhibitors, making them ineffective.

As an alternative strategy the team investigated transcription factors Stat3 and Stat5 which are linked to bcr/abl-induced transformation. The team tested whether Stat3 and Stat5, acting downstream of Bcr-Abl are critical for leukaemia maintenance and if they could be a alternative target for treatment.

"We developed a tumour-specific gene-deletion approach to analyse the roles of Stat5 and Stat3 in Bcr/Abl-induced leukaemia growth," said

Sexl. "We discovered that both factors are required for the development of Bcr-Abl, but once established only Stat5 is crucial for the survival and growth of leukemic Cells."

Even mutated forms of bcr-abl, Leukaemia cells, which are resistant to inhibiting drugs such as Imatinib, are still dependent on Stat5.

"Cancer cells undergo extensive adaptations in their signalling and metabolic pathways, thereby becoming dependent on certain genes," said Sexl. "In fact the activity of these genes can become limiting for a cancer cell."

The term 'Non-oncogene addication' (NOA) has been coined to describe this phenomenon of gene dependency and inhibiting these critical genes within the signalling network is predicted to cause system failure and halt the growth of leukaemia cells.

"In this study we demonstrated that bcr-abl, Leukaemia cells are addicted to Stat5 to maintain the leukameic state, concluded Sexl. "We've identified Stat5 as an Achilles' heel in the signalling network downstream of Bcr-Abl. Thus, inhibition of Stat5 may provide a novel therapeutic approach for treatment of leukaemia."

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