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Researchers make critical leukemia stem cell discovery

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Researchers at King's College London have discovered that leukaemic stem cells can be reversed to a pre-leukaemic stage by suppressing a protein called beta-catenin found in the blood.

They also found that advanced leukaemic stem cells that had become resistant to treatment could be 're-sensitised' to treatment by suppressing the same protein.

Professor Eric So, who led the study at the Department of Haematology at King's College London, says the findings, published today in the journal *Cancer Cell*, represent a 'critical step forward' in the search for more effective treatments for aggressive forms of leukaemia.

The role that beta-catenin plays in the development and drug-resistance of stem cells in acute leukaemia was previously unknown. This study, funded by the Association for International Cancer Research (AICR), Cancer Research UK and the Kay Kendall Leukaemia Fund, reveals its significance and highlights it as a potential therapeutic target that could allow selective eradication of leukaemic stem cells.

King's scientists looked at leukaemic stem cells found in types of leukaemia that involve mutations of the MLL gene. This accounts for around 70 per cent of infant leukaemias and 10 per cent of adult acute leukaemias. The prognosis for this type of leukaemia in children is not good – only 50 per cent survive past two years after receiving standard anti-leukaemia treatment.

To understand how the disease develops, the King's team carried out a series of experiments to look at how pre-leukaemic stem cells (which do not always develop into leukaemia) are different to leukaemic stem cells, which sustain the disease and are likely to be responsible for relapse. They carried out studies in mice, in cultured human cells derived from cord blood, and on human leukaemic cells obtained from two leukaemia patients.

The studies in mice showed that pre-leukaemic cells developed into leukaemic stem cells and induced leukaemia, in part by activation of beta-catenin. But suppression of beta-catenin in leukaemic stem cells reduced leukaemic cell growth, delayed the onset of leukaemia and reversed the stem cells to a pre-leukaemic stage. Furthermore, when beta-catenin was completely inactivated in mice with pre-leukaemic cells, the mice did not develop leukaemia, even though they carried MLL gene mutations.

Researchers then wanted to see how suppression of the beta-catenin protein impaired human leukaemic cells. They found that suppression of the protein in MLL leukaemic cells again diminished their ability to proliferate and renew themselves (an essential part of how leukaemia develops). This confirmed the important role of beta-catenin in the human disease.

The study also revealed a previously unrecognized critical function of beta-catenin in mediating drug resistant properties of leukaemic stem cells. Leukaemic stem cells can become resistant to treatment in some cases but, crucially, this study showed that suppression of beta-catenin in human MLL leukaemic cells made them sensitive again.

Professor Eric So, who led the study at King's, said: 'These results are extremely exciting and represent a critical step forward in the search for more effective treatments for this devastating form of leukaemia. The

findings provide compelling evidence that this protein could be exploited to develop an effective therapeutic target for this form of the disease.

'Most of the current anti-cancer therapies used to treat leukaemia attack healthy blood cells as well as cancerous ones. Interestingly, beta-catenin is not required for normal blood stem cells. So if we can specifically target beta-catenin in the bone marrow, we can have potentially a more effective and less toxic anti-leukaemia therapy that can efficiently eradicate leukaemic stem cells but spares healthy blood stem cells.

'Much more research needs to be done before we can adopt this approach in treating people with leukaemia, but the findings of this study do look promising. We will now investigate the mechanisms behind these molecular changes to find out why beta-catenin is so important in the development of MLL leukaemia, and if we can apply the principle to other types of leukaemia.'

Dr Mark Matfield, AICR's scientific co-ordinator said: 'The whole field of cancer stem cell research is relatively new, but this discovery has the potential to be one of the most useful in this rapidly-advancing area, because it shows us directly how a new treatment could be developed.'

Provided by King's College London