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Research Highlights

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Self-renewing blood and leukaemia cells need hedgehog

Simone Alves[1]

Attacking an alternative pathway might help defeat disease

Cancer cells often hijack developmental signaling pathways to cause uncontrolled growth. This month in *Nature*, Tannishtha Reya and her team from Duke University in Durham, North Carolina, show that hedgehog signaling is essential for maintaining chronic myeloid leukaemia and that blocking this pathway with small molecules might be effective in preventing the disease from recurring[1].

Chronic myeloid leukaemia (CML) occurs after a chromosomal translocation fuses two enzymes that are essential for cell signaling: the BCR serine/threonine kinase and the ABL tyrosine kinase. The primary therapy, Novartis' Gleevec (imatinib), targets part of the ABL kinase. However, the cells that propagate CML appear to be resistant, which would explain why the drug stalls rather than cures the disease. A drug that targeted the propagating cells could potentially prevent patients from relapsing.

Many of Gleevec's competitors target resistant forms of BCR/ABL, but the study's results suggest other options, says Reya. "The interesting thing about identifying alternative pathways is that they could be a potential target in therapy-resistant disease."

To explore the role of hedgehog signaling in CML, Reya's group tinkered with Smoothened (Smo), an essential protein in hedgehog signal transduction, which previous work had shown was crucial for creating BCR-ABL–positive leukaemias that could be propagated through retransplantation[2]. Knocking out Smo in normal haematopoietic stem cells (HSCs) markedly decreased their regenerative capacity, and it had similar effects on leukaemia stem cells. Of mice that carried the BCR-ABL fusion protein and normal Smo, 94% developed CML, whereas only 47% of mice carrying the the BCR-ABL and Smo knockout developed the disease. Further work examined how cells were affected. When Smo was absent, the researchers saw fewer cells that were deemed likely to be CML stem cells (i.e., fewer cells showed high levels of the markers c-Kit and Sca-1 and low levels of the marker Lin). Increasing Smo expression both increased the number of these cells and accelerated disease progression. Together these results strongly indicate that hedgehog activity is required to renew HSCs and propagate CML.

Several small-molecule inhibitors for the hedgehog pathway are in clinical development, says Reya, whose coauthors include some who work for or with drug companies. She went on to show that a naturally occurring plant compound, cyclopamine, which targets the hedgehog pathway by blocking Smo, decreased the CML stem cell population both *in vitro* and *in vivo* and decreased the incidence of disease. Even cells engineered to be resistant to Gleevec could be targeted with cyclopamine, suggesting that combination therapy could be used against drug-resistant CML. Moreover, targeting the hedgehog pathway was also effective in late-stage human CML cells.

"Studies like this are very important for informing us how to use hedgehog inhibitors in the clinic," says William Matsui of The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital in Baltimore, Maryland. Using a hedgehog inhibitor in conjunction with Gleevec, which targets the bulk of the tumour, could be extremely effective at eradicating CML. Reya wants to do more in-depth human work next, which Matsui agrees is essential, adding that it will be interesting to find out what role hedgehog signaling plays in the bulk of the tumour cells. "Clinical research is expensive and time consuming, so the more information we have going into a study, the better," he says.

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References

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