

 CANCER STEM CELLS

Killing Hedgehog to treat CML

Most cases of chronic myeloid leukaemia (CML) are caused by a chromosomal translocation that creates a fusion protein between breakpoint cluster region (BCR) and the tyrosine kinase *ABL1*. The tyrosine kinase inhibitor *imatinib* blocks CML progression; however, patients who harbour a BCR-*ABL1*^{T315I} point mutation are resistant to this drug and other tyrosine kinase inhibitors. A report in *Nature* now identifies a potential new therapeutic strategy for this disease. Tannishtha Reya and colleagues have shown that inhibition of the hedgehog (Hh) signalling pathway reduces the number of normal and malignant haematopoietic stem cells (HSCs) and blocks CML propagation.

To evaluate the role of Hh signalling in CML, Reya and colleagues developed mice that lacked

expression of smoothened (SMO), the transmembrane protein that transmits Hh signals, in haematopoietic cells. The frequency of HSCs and differentiated cells was unaffected by SMO loss, but HSC renewal was severely impaired. Furthermore, the loss of SMO decreased cancer incidence and increased latency in a mouse model of CML, whereas transgenic expression of an activated form of SMO increased the number of CML cancer stem cells and accelerated cancer progression. Thus, Hh signalling positively regulates normal and malignant stem cell propagation.

Cyclopamine, which stabilizes inactive SMO and inhibits Hh signalling, reduced the ability of primary human blast crisis CML cells and mouse CML stem cells to form colonies *in vitro*. In addition,

irradiated mice transplanted with BCR-*ABL1*-expressing HSCs had a reduced CML stem cell population and prolonged survival when treated with cyclopamine. Importantly, cyclopamine also slowed the progression of imatinib-resistant CML in mice and reduced colony formation of imatinib-resistant human CML cell lines. Therefore, targeted inhibition of Hh signalling could be useful for overcoming imatinib resistance in CML.

This study provides evidence that Hh inhibition impedes CML progression by affecting CML stem cells. Hh signalling is active in several haematological malignancies, and it will be important to determine whether inhibition of Hh signalling is beneficial in these diseases and solid tumours. Intriguingly, the authors found that *Smo*^{-/-} CML stem cells expressed higher levels of the Notch pathway inhibitor NUMB, and ectopic expression of NUMB blocked their propagation. As the authors' previous studies linked high levels of NUMB to HSC differentiation, these data suggest that NUMB expression as a result of inhibiting Hh may contribute to the depletion of cancer stem cells by promoting differentiation. The mechanistic details that link SMO loss to NUMB expression await further study.

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