LEUKAEMIA

Targeting silent cells

Disease relapse is a major obstacle to curing patients with leukaemia. Current therapies effectively target dividing cells, but a small population of quiescent leukaemia-initiating cells (LICs) are thought to be responsible for re-initiating malignancy upon

drug discontinuation. Writing in *Nature*, Pandolfi and colleagues now show that promyelocytic leukaemia protein (PML) is required to maintain the quiescence of these cells in chronic myeloid leukaemia (CML), and that pharmacological inhibition of PML could represent a promising therapeutic strategy.

Previous studies have shown that PML functions as a tumour suppressor, but its role in haematopoietic stem cells (HSCs) and LICs — which share properties including pluripotency and quiescence — is poorly understood. In this study, Pandolfi and colleagues showed that PML is highly expressed in both HSCs and LICs and that, contrary to solid tumours, low levels of PML expression correlate with better clinical outcome in patients with CML.

The authors then investigated the function of PML in HSCs and LICs using *PML*-deficient cells. These studies indicated that chronic *PML* deficiency resulted in progressive impairment of HSC function due to defective maintenance of quiescence. Moreover, *PML*-deficient LICs undergo intensive cell cycling, resulting in impairment of LIC maintenance.

Interestingly, arsenic trioxide (As_2O_3), a traditionally used therapeutic agent for the treatment of

leukaemia, has been shown to target PML for degradation. Indeed, when the authors analysed the effects of As_2O_3 in wild-type HSCs and LICs *in vitro*, they found that it reversibly decreased PML expression and impaired HSC quiescence *in vivo*.

Finally, as agents that enhance cycling of quiescent, chemotherapy-insensitive LICs are expected to aid LIC elimination, the authors assessed the effects of combining As_2O_3 (to mimic the effect of PML loss) with the traditional chemotherapeutic cytosine arabinoside (Ara-C) in serial transplantation assays in mice and on cultures of human LICs. As_2O_3 significantly enhanced the effect of Ara-C on cell apoptosis and significantly increased mouse survival.

On the basis of their studies, Pandolfi and colleagues propose that As_2O_3 or novel PML-lowering drugs could be used transiently at leukaemia onset together with, or followed by, standard therapies. Further investigations of the role of PML in other cancers might also indicate new opportunities for targeting cancer-initiating cells.

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ORIGINAL RESEARCH PAPER Ito, K. *et al.* PML targeting eradicates quiescent leukaemia-initiating cells. *Nature* 11 May 2008 (doi: 10.1038/nature07016).

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