LEUKAEMIA

A provoking end?

There is good evidence that leukaemia-initiating cells (LICs) are responsible for tumour initiation and maintenance, and probably for relapse and resistance to therapy. LICs are thought to be largely quiescent, meaning that they are not affected by therapies that target dividing tumour cells. Pier Paolo Pandolfi and colleagues now have evidence that the tumour suppressor protein PML helps to maintain this inert state and that degradation of PML is one means with which to induce these cells to enter the cell cycle and become sensitive to standard chemotherapy regimens.

PML is commonly associated with acute promyelocytic leukaemia (APL), where its translocation results in the formation of the PML–RARα (retinoic acid receptor α) fusion protein that blocks myeloid cell differentiation. APL patients can be successfully treated with agents that negate the effect of the fusion protein, such as arsenic-based drugs that induce degradation of PML and PML–RARα or exogenous retinoic acid. To understand more about the function of PML in leukaemia, Pandolfi and colleagues analysed the expression of PML in mouse haematopoietic cells. The haematopoietic stem cell (HSC) population showed high levels of PML expression, as determined by western blot and immunofluoresence. They also found that PML is highly expressed in blasts obtained from patients with chronic-phase chronic myeloid leukaemia (CML) and that expression of PML correlates with patient outcome: low levels indicate an increased response to therapy and increased overall survival.

So how does PML affect the HSC population? The authors found that 8-week-old *Pml*$^{-/-}$ mice had increased numbers of HSCs and that the number of quiescent HSCs was reduced compared with wild-type mice. Subsequent experiments indicated that this reduction in quiescence correlated with stem cell exhaustion, suggesting that PML suppresses proliferation in HSCs, which is compatible with their long-term survival. This effect also translates to LICs: BCR–ABL-expressing LICs that lacked PML expression were unable to repeatedly induce a CML-like disease in serial bone marrow transplant assays in mice. Importantly, LICs treated with arsenic trioxide (As_2O_3) were induced into the cell cycle owing to the degradation of PML and this, in combination with cytosine arabinoside, resulted in the death of LICs *in vitro* and *in vivo*. Importantly, As_2O_3 treatment did not seem to adversely affect the function of normal HSCs in mice or in human HSCs *in vitro*, and this drug has minimal toxicity when used in the treatment of APL.

Therefore, targeting PML in LICs, in combination with other therapies such as imatinib, might prove a viable option in patients with CML. Moreover, As_2O_3-induced PML degradation has recently been shown to be mediated by RNF4, a SUMO-dependent E3 ubiquitin ligase, suggesting other potential therapeutic routes to achieve degradation of PML.

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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)

FURTHER READING Tatham, M. H. *et al.* RNF4 is a poly-SUMO-specific E3 ubiquitin ligase required for arsenic-induced PML degradation. *Nature Cell Biol.* **10**, 538–546 (2008) | Lallemand-Breitenbach, V. *et al.* Arsenic degrades PML or PML–RARα through a SUMO-triggered RNF4/ubiquitin mediated pathway. *Nature Cell Biol.* **10**, 547–555 (2008)

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