THERAPY

Modifying MYC expression

> targeting BRD4 may be a common mechanism by which to inhibit MYC in AML.

Acute myeloid leukaemia (AML) is characterized by cooperative genetic and epigenetic alterations that promote tumorigenesis through various mechanisms, including the deregulation of differentiation programmes. Chromatin modifiers have been implicated in regulating such pathways; so, Lowe, Vakoc and colleagues carried out an RNA interference (RNAi) screen to identify key regulators of epigenetic modification in AML.

Zuber, Shi and colleagues constructed a short hairpin RNA (shRNA) library targeting 243 known regulators of epigenetic histone modifications. The library was transduced into a mouse model of AML (driven by MLL-AF9 and NRAS-G12D), and after 14 days the authors assessed which shRNAs were depleted by more than 20-fold (indicating that the shRNA target inhibits AML growth). Of the 177 depleted shRNAs, those targeting bromodomain containing 4 (*Brd4*) were one of the most strongly depleted. Knockdown of BRD4 expression induced cell cycle arrest and apoptosis in leukaemia cell lines and in MLL-AF9^{+} human AML cell lines but had modest effects on normal cells, indicating that BRD4 could be a good target for AML that harbours the MLL-AF9 translocation. Indeed, the authors found that JQ1 — a small-molecule inhibitor of BRD4 — inhibited growth and induced apoptosis of leukaemia cells with MLL fusions, 13 of 14 AML cell lines and 12 of 15 primary human AML samples. This indicated that BRD4 has a crucial role in AML pathogenesis; so, the authors investigated its role in AML *in vivo*. They found that knockdown of *Brd4* after disease induction in *Mll-Af9*;*Nras*^{G12D} mice delayed leukaemia progression and improved survival, indicating that BRD4 could be an effective therapeutic target. So, they treated mice transplanted with MLL-AF9;NRAS-G12D leukaemia cells with JQ1, and found that daily injection delayed leukaemia progression and significantly increased survival. Moreover, JQ1 had anti-leukaemic activity in a mouse model of AML driven by AML1-ETO9A, NRAS-G12D and loss of p53.

MYC has previously been implicated as a target of BRD4, thus Zuber, Shi and colleagues investigated whether MYC was affected by JQ1-mediated inhibition of BRD4. They found that MYC protein and mRNA expression was substantially reduced in MLL-AF9;NRAS-G12D-induced AML that was treated with JQ1. Chromatin immunoprecipitation experiments showed that BRD4 binds the *Myc* promoter and that this binding — and MYC target gene expression — was abrogated on treatment with JQ1. Downregulation of MYC was observed in several subtypes of AML cells from human and mouse, suggesting that targeting BRD4 may be a common mechanism by which to inhibit MYC in AML.

Therefore, the clinical development of second-generation BRD4 inhibitors that have better pharmacokinetics might be a promising way to inhibit MYC and other BRD4-regulated pathways that mediate leukaemogenesis.

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ORIGINAL RESEARCH PAPER Zuber, J. *et al.* RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. *Nature* 3 Aug 2011 (doi:10.1038/nature10334)
FURTHER READING Zuber, J. *et al.* An integrated approach to dissecting oncogene addiction implicates a Myb coordinated self-renewal program as essential for leukemia maintenance. *Genes Dev.* **25**, 1628–1640 (2011)