SPECIAL REPORT

Targeting leukemia stem cells with HDAC inhibitors and modulators of the DNA damage response

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Leukemia Supplements (2014) 3, S14–S15; doi:10.1038/leusup.2014.8**Keywords:** Histone deacetylase inhibitors; NAE inhibitors; MLN4924; Wee1; leukemia stem cells; leukemia-initiating cells; DNA damage response

Histone deacetylase inhibitors (HDACIs) are epigenetic agents that modify chromatin structure and by extension, gene expression.¹ Moreover, recent evidence suggests that such agents may target leukemia stem cells.² Recently, attention has focused on mechanisms of action other than or in addition to histone modifications to account for their anti-neoplastic activity.³ For example, the association between HDACI activity and induction of DNA damage has long been recognized.⁴ This may reflect the ability of HDACIs to perturb each of the three arms of the DNA damage response (DDR), for example, DNA damage checkpoints, DNA repair—including both homologous recombination (HR) and non-homologous end-joining repair—and apoptosis induction.⁵ Of note, disruption of non-homologous recombination by HDACIs⁶ may be particularly important for non-cycling G0 cells such as stem cells.⁷

These considerations raise the possibility that agents that disrupt one or more of the components of the DDR might be used to enhance the anti-leukemic activity of HDACIs, and that primitive leukemia-initiating cells may be vulnerable to this strategy. For example, it has been reported that interruption of Chk1, which has an important role in the DNA damage checkpoints, may modify neoplastic responses to HDACIs.⁸ More recently, pharmacological or genetic disruption of Chk1 was shown to enhance HDACI lethality toward human leukemia cells, an effect independent of p53 status.⁹ Notably, interference with Chk1 may have cooperated with HDACI-mediated disruption of HR repair proteins (for example, BRCA1) to promote DNA damage and cell death. Importantly, populations of cells enriched for leukemia-initiating cells (for example, CD34+, CD38– and CD123+) were susceptible to this strategy. To extend these findings, studies were performed to determine whether similar events might occur with disruption of the DNA damage checkpoint protein Wee1. Wee1 has classically been associated with the G2M checkpoint, although recent findings have implicated it in the intra-S phase checkpoint as well.¹⁰ Preliminary studies suggest that analogous to Chk1 disruption, interference with Wee1, either genetically or pharmacologically, significantly enhances the anti-leukemic activity of HDACIs both in p53-null or wild-type cells and in primitive populations.

Another candidate class of DNA damage-disrupting agents includes NEDD8-activating enzyme (NAE) inhibitors, of which the prototype, MLN4924, has recently been shown to exhibit significant anti-leukemic activity both preclinically¹¹ and in patients with refractory leukemia.¹² NAE inhibitors induce DNA damage by promoting DNA re-replication, and elicit strong DDR checkpoint responses.¹³ Early evidence suggests that NAE inhibitors may interact

reciprocally with HDACIs, which can attenuate checkpoint responses, to promote DNA damage and cell death. Of note, primitive leukemia progenitors appear to be vulnerable to this strategy.

Taken together, these findings argue that in addition to rational combinations involving standard chemotherapy, hypomethylating agents or other targeted agents (for example, kinase inhibitors), consideration should be given to the use of disruptors of the DDR to potentiate the anti-leukemic activity of HDACIs. They also raise the possibility that populations enriched for primitive leukemia-initiating cells may be particularly vulnerable to this strategy.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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