



Commentary

MAP4K1 expression is a novel resistance mechanism and independent prognostic marker in AML-but can be overcome via targeted inhibition

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Acute myeloid leukemia (AML) is an aggressive hematologic malignancy, characterized by the clonal accumulation of un-or-poorly differentiated myeloid-lineage cells [1]. Rapid advancements in cytogenetic and molecular techniques have allowed an ever-improving understanding of the mechanistic underpinnings of this disease [2]. Recent AML classification schemata also utilize these advances [2]. In parallel, novel therapeutic agents have been identified or developed to specifically target these oncogenic drivers [3]. However, despite these evolutions, the prognosis for AML remains poor [4]. Additionally, the ability of leukemic blasts to evolve and evade targeted therapeutic agents is well described [3].

Although these new drugs are promising additions to the therapeutic armamentarium, important caveats exist. Many mutations do not have a specific targeted therapy, or may result in intolerable side-effects when targeted [1,3]. Alternatively, patients may lack identifiable, targetable molecular drivers [2]. These agents have generally been tested only in the context of relapsed/refractory disease, and integration with front-line therapeutic strategies is an ongoing but lengthy process [3]. Finally, for many of these drugs, the identification of novel resistance and escape mechanisms often occurs shortly after treatment initiation, particularly when used as monotherapy [3,5]. Consequently, novel combinatorial therapeutic strategies and identification of resistance mechanisms to those strategies are warranted.

Homoharringtonine (HHT) is a cytotoxic alkaloid derived from plants of the *Cephalotaxus* genus [6]. It has demonstrable efficacy against multiple malignancies including AML and Chronic Myeloid

Leukemia (CML) [6,7]. It was approved by the U.S. Food and Drug Administration (FDA) in 2012 for adult patients with CML, with resistance and/or intolerance to two or more tyrosine kinase inhibitors [6]. In the former context, a phase III randomized controlled trial of previously untreated AML patients found significantly improved 3-year event free survival and complete remission rates in patients receiving homoharringtonine/cytarabine/aclarubicin versus daunorubicin/cytarabine [7]. However, the mechanisms of HHT-resistance are not well understood, nor are the clinical implications of that resistance.

In their recently published study, Ling et al [8] sought to address resistance mechanisms to HHT. After creating an HHT-resistant cell line, differences in gene expression between the resistant and wild-type cells were analyzed. They identified differential expression of mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1). Intriguingly, they showed that MAP4K1 expression corresponds to HHT sensitivity of a variety of AML cell lines. Analysis of MAP4K1 expression in primary patient samples revealed several things. First, MAP4K1 expression was associated with significantly poorer overall survival, event-free survival, and relapse-free survival. Second, patients with AML had significantly higher MAP4K1 expression than those without. Moreover, MAP4K1 expression levels did not correlate with the presence of any identifiable patient characteristics or mutations (including those with prognostic/clinical relevance). Furthermore, multivariate analysis showed that, even after adjusting for known prognostic markers, higher expression remained a significant, independent negative prognostic factor. Murine xenograft models were generated and based on the improved survival of MAP4K1 knockdown mice, this finding, was replicated *in vivo*. Taken together, these are notable findings, as expression of the MAP4K1 protein has not previously been identified as either a mechanistic or prognostic marker in AML. It is, however, targetable. A selective, small molecule kinase inhibitor has recently been developed and when combined with PD-1 checkpoint blockade, shows significant enhancements in CD8+ T-cell anti-tumor activity [9]. Additionally, MAP4K1 has been shown to be immunosuppressive, with negative effects on both CD4+ and CD8+ T-cell function and, by inhibiting this axis, the efficacy of adaptive cellular therapies (e.g. chimeric antigen receptor T-cells; CAR-T) can be enhanced [10]. As such, Ling et al's elucidation of

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MAP4K1's role in AML carries intriguing potential implications, which may have therapeutic relevance.

Delving further, Ling et al identified a mechanism by which MAP4K1 may exert its effects. p21 and p27 are cell-cycle inhibitors capable of inducing G0/G1 arrest. Their expression levels appear to be modulated by MAP4K1 – specifically, MAP4K1 knockdown results in increased p21 and p27 expression and slows leukemia proliferation, while MAP4K1 overexpression results in lessened p21 and p27 and accelerates proliferation. The authors also found that MAP4K1 alters expression of multiple proteins involved in DNA damage/repair pathways. Taken together, these mechanisms ultimately suggest that MAP4K1 facilitates AML expansion by allowing AML cells to progress uninhibited through the cell-cycle checkpoints. Finally, they also uncovered a strategy to overcome that resistance. The combination of HHT plus sunitinib has not been previously utilized, but herein demonstrated a high degree of combinatorial synergy against both AML cell lines and primary patient samples.

As the treatment paradigm for AML continues to evolve, comprehensive evaluations such as this are necessary to not only identify novel, drug-able targets, but also to elucidate mechanisms of treatment resistance and the means by which they can be overcome. Having now been identified as such a target, the combination of targeted MAP4K1 inhibition with HHT has potential direct translational relevance. While the role and integration of these agents into existing regimens remain to be clarified, this study is an important step.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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