Metallothionein 1: the Achilles heel of *Dnmt3a;Npm1*-mutant acute myeloid leukemia

Bowen Yan[1,2] and Olga A. Guryanova[1,2]

[1]Department of Pharmacology & Therapeutics, University of Florida College of Medicine and [2]University of Florida Health Cancer Center, Gainesville, FL, USA

Correspondence: O.A. Guryanova
oguryanova@ufl.edu

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In this issue of *Haematologica*, a study by Colom Díaz *et al.*[1] propels Metallothionein 1 (MT1) into the spotlight as a newly identified mediator of malignant cell growth in a model of *Dnmt3a;Npm1*-mutant acute myeloid leukemia (AML) and in human disease. AML remains a deadly malignancy despite significant advances in diagnosis, therapy, and supportive care, with a 5-year survival rate for adults in the United States of about 33%.[2] While presence of *NPM1* mutations is generally associated with favorable outcomes, co-occurring mutations in *DNMT3A* confer a more grim prognosis due to increased risk of relapse,[3,4] emphasizing the urgent need for new mechanism-driven targeted strategies in this patient population.

Mt1 is a low molecular weight, cysteine-rich intracellular protein that is widely expressed across most organs. It plays a crucial role in maintaining cellular metal ion homeostasis, including regulating metal balance, alleviating heavy metal toxicity, and defending against oxidative stress, inflammation, and other environmental insults and stressors.[5,6] This study adds a new role to

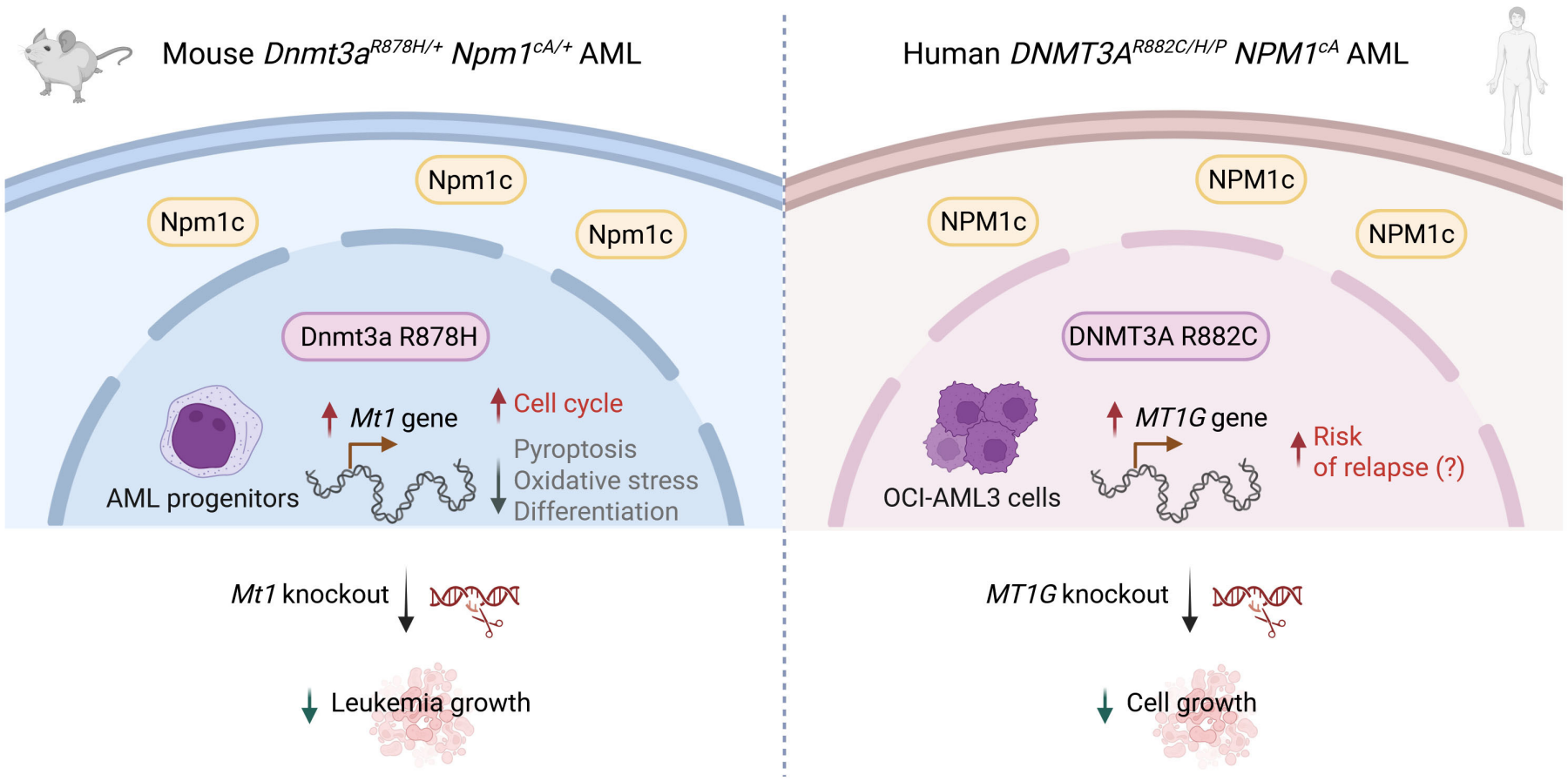

Figure 1. Mt1 is a dependency in mouse and human *Dnmt3a;Npm1*-mutant acute myeloid leukemia. This schematic illustrates the differential expression and functional impact of metallothionein isoforms in mouse and human acute myeloid leukemia (AML) harboring DNMT3A and NPM1 mutations. In mouse AML cells (left), co-occurrence of *Dnmt3a*$^{R878H/+}$ and *Npm1*$^{cA/+}$ leads to increased expression of *Mt1*, and its knockout results in decreased cell growth. In human AML cells (right), co-mutated *DNMT3A* $^{R882C/+}$ and *NPM1*$^{cA/+}$ drive upregulation of *MT1G* expression, and knockout of *MT1G* similarly reduces cell growth.

its list of responsibilities - safeguarding AML cells from ferroptotic death.

This study identifies *Mt1* as one of the top genes uniquely expressed in *Dnmt3a;Npm1*-mutant AML progenitors compared with other molecular disease subtypes and normal bone marrow counterparts. *Mt1* expression is critical for the survival of leukemia cells: thus, disrupting *Mt1* in *Dnmt3a;Npm1*-mutant AML by CRISPR-Cas9-sgRNA complexes (RNP) decreased cell proliferation *in vitro* and delayed disease progression in animal models. Interestingly, elevated *Mt1* was highly specific to *Dnmt3a;Npm1*-mutant AML as it was not observed in cells with *Dnmt3a* or *Npm1* single-gene alterations alone, indicating cooperativity of both mutations as a critical mechanism to achieve transcriptional upregulation of *Mt1*.

Unlike a single *Mt1* gene in mice, humans feature eight functional MT1 paralogs: MT1A, MT1B, MT1E, MT1F, MT1G, MT1H, MT1M, and MT1X.[7] Among these, only *MT1F*, *MT1G*, *MT1H* and *MT1X* show increased expression in human AML compared to normal bone marrow samples.[1] In the human OCI-AML3 cell line, a well-established model of *DNMT3A;NPM1*-mutant AML, *MT1G* is highly expressed compared to normal bone marrow cells. Furthermore, disruption of *MT1G* decreases viability exclusively in *DNMT3A;NPM1*-mutant AML cells, but not in OCI-AML2 cells with *DNMT3A* mutation alone. These findings firm up *MT1G* as a specific dependency in AML with *DNMT3A* and *NPM1* co-mutation, that is not observed with *DNMT3A* mutation alone (Figure 1).

In conclusion, the study by Colom Díaz *et al*. identifies MT1 as a novel vulnerability in *Dnmt3a;Npm1*-mutant AML, highlighting a previously underappreciated role of metal metabolism in the pathophysiology of leukemia. Their findings suggest that targeting MT1 may selectively impair malignant cells while sparing normal hematopoiesis, offering a promising pathway for future precision therapies. However, limitations remain. The exact mechanism whereby *DNMT3A* and *NPM1* mutations cooperate to regulate *Mt1* expression requires further investigation. Additionally, no pharmacological inhibitors for Mt1 or MT1G are currently available. This study represents a timely call for the research community and industry partners to transform this newly identified metabolic mechanism co-opted by leukemia into a targetable vulnerability. The challenge ahead is to rapidly advance these discoveries toward clinical translation, for the benefit of AML patients.

Disclosures

No conflicts of interest to disclose.

Contributions

BY and OAG wrote the manuscript.

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