The TRIM31 paradox: an unexpected benefit for leukemia stem cells

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Acute myeloid leukemia (AML) is an aggressive blood cancer that arises due to mutations in hematopoietic stem cells (HSC). AML is genetically heterogeneous, and this genetic information is now used in the clinic to determine prognosis and for targeted therapeutic intervention where appropriate. Conversely, post-translational factors that regulate AML growth and survival, such as the role of E3 ubiquitin ligases, are less well understood.

E3 ubiquitin ligases are mediators of protein ubiquitination and consequent degradation, acting via recruitment of an E2 ubiquitin conjugating enzyme to a recognized substrate. The polyubiquinated substrate is then marked among others for proteasome degradation and its role is described in cell cycle regulation and numerous other biological processes.

Among the hundreds of E3 ligases, few have been studied

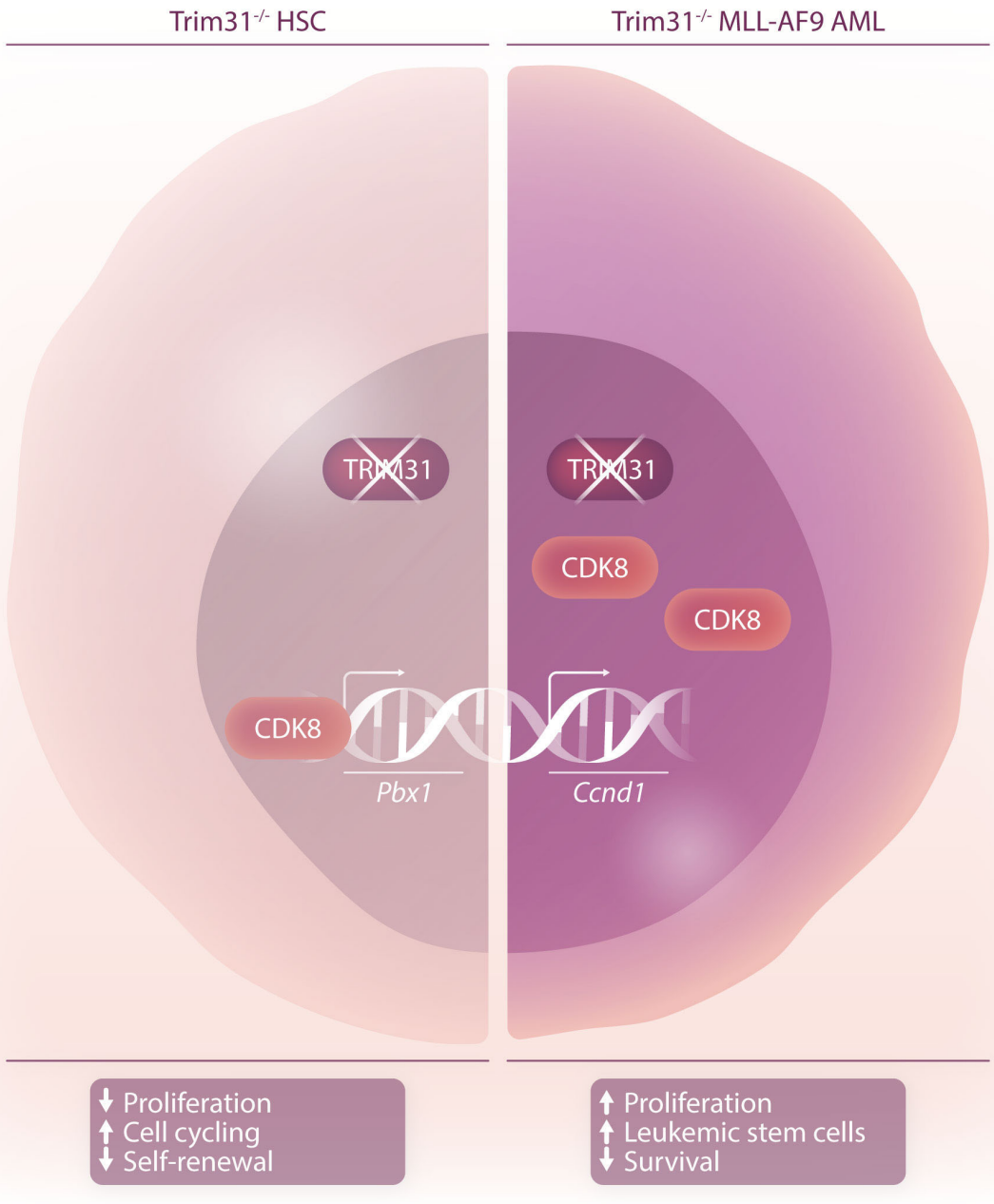

Figure 1. Loss of Trim31 has distinct effects on normal and malignant hematopoietic stem cells. Trim31-loss leads to accumulation of CDK8 in the cells leading to upregulation of Pbx1 and Ccnd1. In normal hematopoietic stem cells (HSC) this results in increased cell cycling with loss of proliferation and self-renewal capacity. On the contrary, in MLL-AF9-driven acute myeloid leukemia (AML) cells, Trim31-loss leads to increased proliferation, expansion of leukemic stem cells, and reduced survival through more aggressive disease.

in the hematopoietic system but these have an important role in HSC self-renewal capacity and hematopoietic stem cell homeostasis. For example, loss of E3 ubiquitinase Fbw7 leads to differential expression of mediators of cell cycle entry (Myc, Notch1, cyclin E), loss of stem cell quiescence and HSC self-renewal capacity, and depletion of HSC.[1] Loss of E3 ubiquitin ligase Itch, although also driving a hyperproliferative HSC phenotype, was also superior in maintaining HSC repopulation capacity.[2] Levels of the E3 ubiquitin ligase TRIM31 impact prognosis and progression in solid cancers.

In the report published in Haematologica, Zhang *et al.*[3] sought to determine whether the loss of TRIM31 impacted normal hematopoiesis and the development of leukemia. Using a series of phenotypical analysis and transplantation assays, they demonstrated that TRIM31 was required for long-term (LT)-HSC maintenance and competitive repopulation capacity. This functional change was mediated by increased cell cycling and failure to retain a quiescent LT-HSC population that is required to maintain HSC recovery.[4]

Next, the authors sought to use publically available patient gene expression and clinical data to validate these findings. This revealed that patients with low TRIM31 expression had inferior overall survival and, interestingly, this was mostly found in patients with *MLL*-translocated AML. This unexpected finding prompted the authors to assess the effect of TRIM31 loss in a model of *MLL*-translocated AML. Consistent with this human data, but in contrast to the findings in normal hematopoiesis, loss of TRIM31 actually accelerated MLL-AF9-induced AML.

The authors examined the underlying mechanism by which TRIM31 loss drives HSC functional decline. First, to identify substrates of TRIM31, they performed mass spectrometry in wild-type (WT) and TRIM31$^{-/-}$ cells. CDK8 was a direct interaction partner of TRIM31 and was substantially more abundant upon loss of TRIM31. Consistently, CDK8 ubiquitination was decreased in TRIM31$^{-/-}$ cells. To confirm the role of CDK8 activation in LT-HSC functional decline, Zhang *et al.* used a CDK8 inhibitor and genetic approaches to modulate CDK8. In both cases they were able to restore LT-HSC function, which was evident through increased donor-derived chimerism in blood and the HSC compartment. It remains to be determined what the key factors are that regulate TRIM31 expression in AML.

Altogether, this work shows that loss of TRIM31 has distinct and opposite effects in normal and malignant hematopoiesis (Figure 1). As these pathways can now be targeted therapeutically, this work also identifies a need for further study examining how various E3 ubiquitin ligases control cell cycle and HSC/AML function.

With the advent of next generation sequencing, there have been major breakthroughs in understanding recurrent genetic mutations and prognostic schemas,[5] and targeted therapies (e.g., FLT3 inhibitors). This work highlights the importance of understanding protein stability and degradation through ubiquitin ligases in AML, particularly how this might lead to cell cycle dysregulation and, potentially, chemotherapy resistance in AML.[6]

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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