Polycomb protein RING1A limits hematopoietic differentiation in myelodysplastic syndromes


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Abstract

Genetic lesions affecting epigenetic regulators are frequent in myelodysplastic syndromes (MDS). Polycomb proteins are key epigenetic regulators of differentiation and stemness that act as two multimeric complexes termed polycomb repressive complexes 1 and 2, PRC1 and PRC2, respectively. While PRC2 components such as ASXL1 and EZH2 are frequently mutated in MDS and AML, little is known about the role of PRC1.

To analyze the role of PRC1, we have taken a functional approach testing PRC1 components in loss- and gain-of-function experiments that we found overexpressed in advanced MDS patients or dynamically expressed during normal hematopoiesis.

This approach allowed us to identify the enzymatically active component RING1A as the key PRC1 component in hematopoietic stem cells and MDS. Evaluating its pharmacologic inhibition indicated that RING1A has limited potential as drug target.

Genetic perturbation studies in AML/MDS cells identify RING1A as key PRC1 component

The influence of RING1A on differentiation is isoform-specific

Suppression of RING1A favors differentiation of hematopoietic progenitors

Conclusion

RING1A is expressed in CD34+ bone marrow cells and further overexpressed in high-risk MDS patients. Knockdown of RING1A in an MDS-derived AML cell line facilitated spontaneous and retinoic acid-induced differentiation. Similarly, inactivation of RING1A in primary CD34+ cells augmented erythroid differentiation. Treatment with a small compound Ring1 inhibitor reduced the colony forming capacity of CD34+ cells from MDS patients and healthy controls. In MDS patients higher RING1A expression associated with an increased number of cytopenias and blasts. Our data suggests that RING1A is deregulated in MDS and plays a role in the erythroid differentiation defect. Inhibition of RING1A does not allow to discriminate between healthy and disease cells limiting its therapeutic potential.

Main funding

RING1A is an enzyme and thus a potential drug target. We decided to assess its therapeutic potential by comparing the impact of a compound inhibitor on primary CD34+ bone marrow cells from MDS patients and healthy donors. A. Control experiment on SKK-1. Cells were transfected with shRNA cassettes for RING1A, RING1B and a control hairpin (sh ctrl). B. We have gain overexpression of RING1A in an MDS-derived AML cell line facilitated spontaneous and retinoic acid-induced differentiation. Similarly, inactivation of RING1A in primary CD34+ cells augmented erythroid differentiation. Treatment with a small compound Ring1 inhibitor reduced the colony forming capacity of CD34+ cells from MDS patients and healthy controls. In MDS patients higher RING1A expression associated with an increased number of cytopenias and blasts. Our data suggests that RING1A is deregulated in MDS and plays a role in the erythroid differentiation defect. Inhibition of RING1A does not allow to discriminate between healthy and disease cells limiting its therapeutic potential.