ELSEVIER

Blood 142 (2023) 5717

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

603.LYMPHOID ONCOGENESIS: BASIC

CHD4 Promotes Tumor Formation, Survival, and Resistance to Genotoxic Therapeutics in TP53 Mutant T-Cell Acute Lymphoblastic Leukemia Cells through the NuRD Chromatin Remodeling Complex

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T-Cell acute leukemia(T-ALL) though generally responsive to current chemotherapy remains incurable in over 50% of adult patients. Importantly, the survival for patients with TP53 mutant T-ALL disease is less than 10%. We have previously shown the role of the Methyl Binding Domain protein 2-Nucleosome Remodeling and Deacetylase (MBD2-NURD) chromatin remodeling complex in triple negative breast cancer cell growth and the role of the NuRD component, Chromatin-helicase-binding protein 4(CHD4), in tumor colony formation and genotoxic resistance in acute myeloid leukemia.

In the present study, we have examined the role of specific NuRD complexes and CHD4 in T-cell acute leukemia cells with mutant TP53. The prototypical NuRD complex possesses both a histone deacetylase (HDCC) sub-complex and an ATPase chromatin remodeling sub-complex containing CHD4 linked to MBD2 or MBD3 of the HDCC. CHD4 is linked to the MBD2/3 anchors of the NuRD complex, via GATAD2A or GATAD2B. Depletion of CHD4 was found to increase the rate of apoptosis in several TP53 mutant T-ALL cell lines including Jurkat, MOLT4, RPMI and CCRF by up to 5 to 10-fold. Likewise, depletion of both MBD2 and MBD3 also increased apoptosis and sensitization to the standard genotoxic chemotherapeutic agent, cytosine arabinoside (Ara-C) but had only minimal effects in normal human CD34+ hematopoietic progenitor cells. Depletion of GATAD2B and GATAD2A by shRNA also resulted in a significantly increased survival of 60 days compared to 20 days in Scramble shRNA controls, in a xenogeneic mouse model of T-ALL. Depletion of CHD4 resulted in a profound (10 to 100-fold) decrease in colony formation of the TP53 mutant T-ALL cell lines in methylcellulose. RNA seq analyses identified the apoptosis, ferroptosis and mitophagy pathways as potential mechanisms for the striking effect of NURD disruption on colony formation.

In summary, CHD4, through the NuRD complex, promotes tumor cell formation, survival and therapeutic resistance of TP53 mutant T-ALL cells. Current efforts are aimed at validating these findings in primary T-ALL cells and structure-function studies to advance development of tool compounds for disrupting the NuRD complex, with the long-term goal of developing improved small molecule therapeutics for treatment resistant acute leukemia.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189142