REPORT
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CANCER

EXPLORING AND EXPLOITING THE VARIANTS OF HISTONES AS THERAPEUTIC TARGETS IN ACUTE MYELOID LEUKEMIA

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1. Project summary

Acute myeloid leukemia (AML) is among the most devastating cancers worldwide with an overall 5-year survival rate of less than 30%. Hence, there is an urgent need to research novel approaches than can lead to the development of new therapies that can improve patients' cure.

Epigenetic regulation is a relevant mechanism in AML but still underexploited for the development of therapeutic approaches. Histone variants are important epigenetic regulators, but their involvement and potential as molecular drug targets in AML has not been assessed. The histone variant macroH2A1 in particular is overexpressed in AML, leading to the hypothesis that leukemic cells may have a higher dependency on macroH2A1 than healthy hematopoietic stem cells and could thus be a possible therapeutic target.

The overall aim of this project has been to assess the potential of macroH2A1 histone variants as drug targets in AML, testing the dependence of AML on macroH2A1 and dissecting the molecular mechanisms underlying this function to identify and implement suitable targeting strategies.

2. Main results

Using a mouse model of AML driven by oncogenic MLL-fusion, we determined that macroH2A1 is essential for the development and maintenance of the disease. While deletion of the macroH2A1 encoding gene results in a reduction of leukemia stem cells (LSCs), it does not impair normal hematopoietic stem cell function. This indicates that macroH2A1 could be a novel target to interfere with LSCs, which are main contributors to the disease and are often refractory to chemotherapy treatment, without hindering normal hematopoiesis as a side effect. Importantly, a similar effect has been observed in a model of AML1-ETO9a fusion leukemia, providing evidence that macroH2A1 may promote oncogenicity through maintaining stemness in different LSC-driven AML subtypes.

Using both in vivo mouse models and human AML cell lines, we have identified that macroH2A1 depletion promotes increased mature differentiation features and reduces the regenerating capacity of LSCs. Using transcriptomic analysis, we detected major gene expression changes upon macroH2A1 depletion, including the increased expression of myeloid differentiation gene programs and a decreased expression of gene signatures related to LSC stemness. Moreover, the LSC chromatin accessibility landscape is significantly altered upon deletion of macroH2A1.

To further dissect the molecular mechanism of macroH2A1 function in AML we have conducted rescue experiments with different truncated mutants of the protein. This allowed us to determine which parts of the protein are required to mediate the pro-leukemic function.

In contrast to other histones, macroH2A possesses domains that are accessibly positioned outside of the compact histone octamer core in the context of a nucleosome. Given these structural characteristics, we have selected these domains as main target to initiate the development of an assay suitable for the high-throughput screening of compounds that target macroH2A1 and promote its degradation. Specifically, the assay is based on a gain-of-signal strategy that inversely couples the protein levels of macroH2A1 to the expression of a fluorescent reporter.

Taken together, in this project we have identified macroH2A1 as an epigenetic factor that maintains LSC function in AML through chromatin and gene expression regulation which suggests that it could be a novel target for therapeutic intervention. Moreover, we have identified the functional relevant domain in the context of AML and have initiated the development of assays allowing to screen for degradation-inducing compounds.

3. Relevance and perspective

AML is a hematopoietic malignancy with an overall low survival rate and high percentage of patients relapsing after initial response to chemotherapy. In particular, even very small fractions of resistant residual leukemia stem cells (LSC) after treatment are able to regenerate the leukemic disease and ultimately lead to the death

of the patient. The identification of novel treatment options is an urgent and unmet need.

This research project has identified the histone variant macroH2A1 as a novel factor contributing to AML maintenance through the promotion of LSC function, but dispensable for normal hematopoiesis. This poses macroH2A1 as potential novel target for therapeutic intervention. Notably, we have initiated the development of a screening assay to advance in identifying targeting compounds as a stepping stone towards a possible drug development process.

4. Publications

Hsu CJ, Meers O, Buschbeck M, Heidel FH. The Role of MacroH2A Histone Variants in Cancer. Cancers (Basel). 2021 Jun 15;13(12):3003. doi: 10.3390/cancers 13123003. PMID: 34203934; PMCID: PMC8232725.

The results presented during this project have been presented at the following international conferences:

Event: American Society of Hematology Annual Meeting
Year: 2022
Organizer: American Society of Hematology
Place: New Orleans (USA)
Type of presentation: oral presentation
Presenting author: Chen-Jen Hsu

Event: European Hematology Association 2024 Research Conference
Year: 20224
Organizer: European Hematology Association
Place: Borovets (Bulgaria)
Type of presentation: poster presentation
Presenting author: David Corujo