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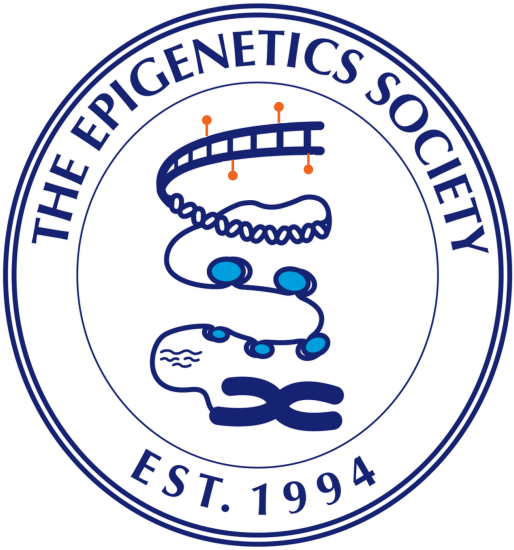

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Table of contents

The epigenetic/transcriptional activity of nuclear mir-223 regulates Flotillin-1 expression and function in myeloid differentiation

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Billi, M., De Marinis, E., Ianni, A., Gentile, M., Quattrocchi, A., Zaza, A., Noguera, N.I., Borello, U., Grignani, F., Nervi, C. The epigenetic/transcriptional activity of nuclear mir-223 regulates Flotillin-1 expression and function in myeloid differentiation.

Abstract

Developmental cell programs, including hematopoietic cell lineage-specification and fate are deeply regulated by epigenetic signals and microRNAs (miRs), the latest mediating the post-transcriptional gene silencing of target mRNAs. However, miRNAs also act as regulators of gene transcription through their interaction with complementary DNA sequences at specific chromatin sites. The nuclear activity of miRs might pave the way for non-coding RNA function in somatic stem cell lineage specification and differentiation. To address this issue, ChIP-sequencing was performed in myeloid cells undergoing granulocytic differentiation to determine, at the whole genome level, the genomic sequences complementarily bound by labelled miR-223 and their enrichment by activating (H3K4me3) and/or repressing (H3K27me3) histone marks. We found that during myeloid differentiation a complex comprising miR-223, RISC component Ago1 and trithorax (TrxG) protein RBBP5 is recruited on an evolutionarily conserved promoter region of Flotillin-1 (FLOT1), containing miR-223 complementary sequences and enriched in H3K4me3 marks. FLOT1 gene encodes a lipid-rafts associated protein, whose role in hematopoiesis is still scarcely characterized. FLOT1 mRNA and protein levels are increased in human hematopoietic progenitor cells undergoing granulo-monocytic differentiation and are altered in acute myeloid leukemia (AML) samples. The recruitment in Flotillin-1-lipid rafts of CSF1R, a growth-factor receptor involved in myeloid differentiation, was increased after CSF1 stimulation. Interestingly, the expression of myeloid differentiation markers CD11b and CD14 are enhanced or inhibited by FLOT1 overexpression or silencing, respectively. Overall, our data suggest nuclear miR-223 as an epigenetic regulator of FLOT1 gene promoter. FLOT1 function appears physiologically related to myelopoiesis and de-regulated in AML.