Altersations in Chromatin Structure Contribute to the Dysregulation of MiRNA-124 in Pulmonary Hypertension

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Rationale

- Pulmonary arterial hypertension (PAH) is a devastating disease without effective treatment, suggesting an urgent need for a better understanding of its pathogenesis (1).
- The important role of reduced expression of miR-124 in modulating the phenotype of pulmonary artery fibroblasts, smooth muscle cells and blood outgrowth endothelial cells from pulmonary hypertensive animals and humans has been demonstrated by our and other groups (2-5).
- Furthermore, we proved that hypertensive fibroblasts (PH-Fibs) exhibited increased HDAC activity (6) and HDAC1, but not DNA demethylation, can restore miR-124 expression in PH-Fibs (2).
- However, little is known regarding the mechanisms contributing to reduced levels of mature miR-124 in PH-cells. A better understanding of the mechanisms responsible for the dysregulated miRNA expression and how HDACi could be working to correct them might offer a better way to treat PH.
- Typically, the level of mature miRNA is controlled via production of precursor miRNA (transcription) and its processing.
- Low levels of precursor miRNA could be due to chromatin condensation and increased methylation of histone H3 on lysine 27 (H3K27) or lack acetylation of H3K27. Defects in processing of miRNA could be due to dysregulation of miRNA processing genes such as Dicer, a central enzyme in miRNA processing.

Objective

To determine the mechanisms contributing to low levels of mature miR-124 in human PH-Fibs by examining miR-124 biogenesis at both the gene transcriptional level (focusing on chromatin structure and H3K27 modification) and miRNA processing level (focusing on miRNA processing genes including Dicer and others).

Results

1. There are no significant difference of miRNA processing gene, Dicer, between CO- and PH-Fibs and no upregulation with HDAC inhibitor treatment in PH-Fibs.

2. The levels of pre-miR-124 were significantly decreased in PH-Fibs compared to CO-Fibs and were restored with HDAC inhibitor treatment (SAHA, Apicidin).

3. PH-Fibs exhibited condensed (closed) chromatin of the miR-124-1 gene, assessed by decreased access/digestion by DNase I

Summary & Conclusion

- We demonstrate here a novel mechanism of miRNA repression in human PH-Fibs. In PH-Fibs, the increased expression of HDAC leads to removal of acetyl residues from H3K27 histones, making H3K27 available for methylation resulting in increased methylation and thus condensed chromatin structure and transcriptional repression of miR-124 expression (A). The addition of HDAC inhibitors prevents the first step of histone deacetylation, and hence the H3K27 cannot be methylated and miR-124 is expressed (B).
- These findings provide further evidences supporting HDAC inhibitors appear to be a promising approach for PH treatment.

References