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FUNCTIONAL ANALYSIS OF HISTONE METHYLATION REGULATORY GENES IN PROSTATE CANCER CELL LINES

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Prostate cancer (PCa) is the most commonly diagnosed malignancy in Europe and the 3rd leading cause of cancer related death among men [1]. The progression of this disease is known to be associated with various epigenetic mechanisms, one of them being gene expression alterations by microRNAs (miRNAs) [2]. They are small, non-coding RNAs which bind to their target mRNAs and decrease gene expression at the post-transcriptional level [3]. Understanding interactions between specific miRNAs and their target genes would help to find novel ways to treat PCa earlier.

In the present study, we focused on histone methylation regulating (HM) genes as potential miRNA targets. Nine HM genes were selected for the analysis based on our previous PCa studies [4; *Maleckaite et al., unpublished data*]. Based on the database search results, potential regulatory miRNAs of the HM genes were identified and the hypothesized regulatory network was created. After evaluating baseline miRNA and HM gene expression levels, two miRNAs – *miR-27a* and *miR-29a* – were selected for loss-of-function *in vitro* experiments in the PC-3 cell line.

Based on the formed miRNA-HM gene regulatory network, *miR-27a* had four potential targets (*KDM1A*, *KDM3A*, *KDM4B*, and *KDM5B*) and *miR-29a* – five targets (*KDM5A*, *KDM5B*, *KDM5D*, *KMT1E*, and *KMT5A*) with one overlapping gene. According to the preliminary data, inhibition of *miR-27a* resulted in increased expression of *KDM4B* and *KDM5B* as expected, while inhibition of *miR-29a* induced upregulation of all its targets except *KDM5D*. Surprisingly, inhibitors of both miRNAs caused downregulation of *KDM3A* indicating a more complex way of HM gene regulation mechanism.

In conclusion, our preliminary data revealed *miR-27a* and *miR-29a* as potential regulators of specific HM genes in PCa. Further experiments would follow to validate these findings, as well as to evaluate cellular effects of the inhibition of the two miRNAs. Satisfying results would lay the basis for the use of *miR-27a* and *miR-29a* inhibitors as prospective PCa therapeutics in the future.

[1] The European Cancer Information System (ECIS) (2023). Cancer cases and deaths on the rise in the EU. European Union. https://joint-research-centre.ec.europa.eu/jrc-news-and-updates/cancer-cases-and-deaths-rise-eu-2023-10-02_en
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