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Sex Hormone–Dependent Regulation of the Renin–Angiotensin System by miR-125b-5p in Brain Cells

Background: Dysregulation of the renin-angiotensin system (RAS) plays a critical role in the development and progression of chronic hypertension and its associated cardiovascular complications. Emerging evidence highlights the therapeutic potential of non-coding RNAs as novel interventions for chronic diseases, including hypertension. Our laboratory's previous research identified microRNA-125b-5p (miR-125b-5p) as a potential regulator of key RAS-related genes, suggesting its involvement in modulating hypertensive mechanisms through epigenetic regulation. In silico analyses further revealed that miR-125b-5p possesses conserved target sites in critical genes such as ACE2 and ATRAP. Based on these findings, the present study investigates the regulatory role of miR-125b-5p in modulating RAS components in response to angiotensin II (Ang II), with a particular focus on the influence of sex hormones.
Methods: To investigate the regulatory role of miR-125b-5p, two brain-derived endothelial cell lines, bEND.3 (mouse) and LUHMES (human) were treated with angiotensin II (Ang II, 100 nM) to mimic hypertensive stress, β-estradiol (E2) to simulate the female hormonal environment, and dihydrotestosterone (DHT) to simulate the male hormonal environment. In the next step, we designed both an agomir and an antagomir specific to this miRNA and tested them in two cell lines. Cells were treated with 20.5 nmol of either the agomir or antagomir in the presence of Ang II to evaluate the functional response of miR-125b-5p. After 48 hours of treatment, cells were harvested, and total proteins were extracted for Western blot analysis.
Results: Our findings demonstrate that the expression of miR-125b-5p was upregulated by Ang II or DHT, with a further exacerbation observed when both stimuli were combined. Furthermore, cells treated with the miR-125b-5p antagomir exhibited a significant increase in ATRAP and ACE2 protein levels ($P < 0.05$). This effect was reversed in cells treated with the miR-125b-5p agomir, indicating a direct regulatory role of this miRNA. Collectively, these results suggest that miR-125b-5p negatively regulates the expression of both ATRAP and ACE2.
Conclusion: These findings indicate that miR-125b-5p negatively regulates the expression of key molecules within the central RAS in both mouse (bEND.3) and human (LUHMES) brain-derived endothelial cell lines. Since ATRAP and ACE2 are critical components of the RAS, their downregulation by miR-125b-5p suggests a potential role for this microRNA in disrupting RAS signaling pathways. The ability of miR-125b-5p to modulate RAS genes at the post-transcriptional level highlights its function as an upstream epigenetic regulator of hypertensive mechanisms. Further in-depth investigations, including *in vivo* studies and analyses of clinical samples, are warranted to validate these findings and to assess the potential of miR-125b-5p as a therapeutic target for the treatment and management of hypertension.