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P-346  Migration-associated microRNAs are dysregulated in endometriosis: potential diagnostic biomarkers

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Study question: What is the role of dysregulated endometrial microRNAs (miRNAs) in the development of endometriosis?

Summary answer: Dysregulated miRNAs in the endometrium of women with endometriosis can also be found in endometriomas and may affect the migratory ability of endometriotic cells.

What is known already: The molecular mechanisms underlying the pathogenesis of endometriosis are poorly understood. One of the hypotheses is that changes in cell properties observed in endometriotic lesions could be initiated already in the endometrium. Dysregulation of miRNAs in the endometrium of women with endometriosis has been reported in previous microarray-based studies. However, little overlap has been seen between published miRNA expression data. Moreover, the potential role of dysregulated miRNAs in the endometrium of women with endometriosis and whether these changes are also present in the endometrioma are largely unknown.

Study design, size, duration: In this experimental case-control study miRNA gene expression in proliferative phase endometrium was compared between 15 women with laparoscopically confirmed endometriosis (stage III–IV) and 17 age-matched controls who were laparoscopically confirmed to be free of endometriosis. Selected miRNAs were further compared between paired proliferative-phase endometrium and endometrioma from a new cohort of women with endometriosis (stage III–IV) and studied in vitro to understand their effect on cell migration.

Participants/materials, setting, methods: Samples were collected during laparoscopic operations performed at Tartu University Hospital, Estonia. Dysregulated endometrial miRNAs were detected with small RNA sequencing and differential gene expression analysis. Target genes and biological pathways were predicted to understand their potential role in the disease. Selected miRNAs were further studied for their expression in endometriomas using qRT-PCR and in vitro for their proliferation and migration ability using a transwell-migration assay after miRNA mimic transfection of the 12Z endometriotic cell line.

Main results and the role of chance: In total, we identified 9 upregulated and 5 downregulated (2 >fold change > 2, FDR < 0.05) miRNAs in the endometrium of women with endometriosis compared to controls. In-silico analyses showed that predicted target genes of the dysregulated miRNAs were significantly enriched in migration-related KEGG pathways such as adhesion junctions, focal adhesion, MAPK, PI3-AKT, and TGF-beta signaling. The most down-regulated miRNA, miR-193b-5p, and the most up-regulated miRNA, miR-374b-5p, were selected for further characterization. Validation of their expression in endometriomas showed a significant up-regulation of both miRNAs compared to paired endometrium (Fold change > 2, FDR < 0.05). Since it has been reported that altered cell migratory ability could be involved in the pathogenesis of endometriosis and our dysregulated miRNA were associated with migration-related pathways, we explored if miR-193b-5p mimic transfection affects the migration capacity of 12Z cells. A 2-fold decrease in cell migration (p-value 0.0021) was observed after 12Z cell mimic transfection. No change in proliferation was demonstrated.

Limitations, reasons for caution: Although our findings both in-silico and in-vitro suggest a link between dysregulated miRNAs and cell migration, further in-vitro studies in primary cells and in-vivo studies in animal models are needed to reveal the specific pathways that these miRNAs regulate to explain the observed functional changes in the context of endometriosis.
Wider implications of the findings: This study gives molecular insight into the pathogenesis of endometriosis, a poorly understood disease, by demonstrating changes in miRNA expression in both the endometrium and endometrioma that potentially can be linked to a changed cell migratory ability. Furthermore, identified miRNAs could be further evaluated as diagnostic biomarkers in larger studies.

Trial registration number: Not applicable