Epigenetic Regulation of Endometriosis-associated pain

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Introduction
We recently showed the mechanistic role for oxidized-lipoproteins present in peritoneal fluid (PF) in the etiology of endometriosis-associated pain. Differential expression of microRNAs is seen in endometriosis patients with pain compared to those without. Our objective was to explore the possibility of oxidized-lipoproteins modulating the microRNAs changes observed in endometriosis-associated pain.
Materials/Patients
Differential expression of microRNAs and their mRNA targets (nociceptive and inflammatory) was determined in PF treated endometrial cell lines. Samples from IRB-approved and consented patients with and without endometriosis or pain was used. These were compared to endometrial cell-lines treated with various forms of oxidized-lipoproteins.
Methods
RNA (including microRNAs) was isolated from endometrial cells (treated with PF or LDL components) and quantitative PCR was used to determine differential expression of microRNAs using commercial Human whole genome mironome arrays. Cell lysates were collected to perform immunoblotting for inflammatory proteins using Human Neuro Discovery protein array and validated using Western blots.

Statistical Analysis
Prism software (GraphPad, Inc., La Jolla, CA) was used for analysis of non-array qPCR data in cell culture studies. All values were expressed as mean ± standard error of the mean (SEM). One-way ANOVA followed by Tukey's post-hoc test was used to detect differences in relative gene expression among treatment groups. P values less than 0.05 were considered significant. Pathway correlations were analyzed using Target Scan and Ingenuity pathway analysis.
Results
Twenty miRNAs were mutually regulated in cells treated with PF from endometriosis patients with pain and with oxidized LDL components. Among these were isoforms of miR-29, miR-181 and let-7. The ox-LDL treatment also produced significant overexpression of microRNA target genes such as nerve growth factor (NGF), interleukin 6 (IL6) and prostaglandin E synthase (PTGES3) and their downstream protein targets Mip1a and MCP1.
Conclusion
This study showed microRNA regulation by oxidized-lipoprotein components present in abundance in the PF of women with endometriosis. Several such miRNAs responsible for targeting nociceptive and inflammatory molecules were downregulated in the presence of LDLs and were similar to that observed in PF treated cells. Our studies suggest a potential for targeting these oxidation-sensitive miRNAs in the treatment of endometriosis-associated pain.

Keywords : oxidative stress, microRNA, inflammation
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