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Dienogest influence on miRNA expression in tumor necrosis factor-? stimulated endometrial stromal cells from women with endometriosis

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Context – MicroRNAs (miRNAs) are a class of endogenous noncoding RNAs that can silence gene expression by either translational repression or direct mRNA degradation. A number of miRNA are dysregulated in eutopic and ectopic endometrium of women with endometriosis. The influence of progestins, in particular of dienogest (DNG) which has recently been shown to have local anti-inflammatory effects, on miRNA expression has not yet been investigated.
Objective – To quantify the expression of inflammatory response and autoimmunity related miRNAs in endometriotic stromal cells from women with endometriosis exposed to the inflammatory cytokine tumor necrosis factor(TNF)-? with or without the progestin DNG.
Methods – Endometrial stromal cells were isolated from endometrial biopsies of 4 women with endometriosis III-IV stage rAFS and cultured in-vitro.
Intervention – Cells were treated with either TNF-? 10 ng/ml and TNF-? 10 ng/ml+DNG 10-5M or no treatment as a control and the miRNA collected. The expression of 84 miRNAs was performed via the miScript miRNA PCR array (Product MIHS-105Z, Qiagen). Curated lists of miRNA influenced by the treatment were assessd for potential target interactions with biological pathways via mirnet.ca and the Reactome database.
Main Outcome Measure – miRNAs fold expression (controls, TNF-? 10 ng/ml and TNF-? 10 ng/ml+DNG). RNU-6, SNORD 61, 68, 72, 95, 96A were used as reference targets.
Results – TNF-? stimulated the stromal cellular production of miRNAs related to inflammatory response and autoimmunity (0.80 vs. 1.36 fold production, $p<0.00001$). We have identified two pools of miRNAs that were more upregulated (n=43, 51.2%, $p<0.00001$), or down regulated to no treatment levels (n=32, 38.1%, $p<0.00001$) when DNG was added to TNF-?. The upregulated miRNAs were significantly linked to collagen and extracellular matrix production, whereas those downregulated were related to cellular response to oxidative stress and senescence and TGF? and FGFR signaling pathways.
Conclusions - miRNAs have an important role in the pathophysiology of inflammatory diseases, such endometriosis, by targeting different genes in a tissue and cell specific manner. TNF? increases their production in endometriotic stromal cells. The concomitant effect of DNG on their production could influence the local effects of these compounds at the disease location.

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