Activated Platelets Induce Hypoxia-inducible factor-1alpha (HIF-1α) Expression through TGF-β1 in Human Endometrial Stromal Cells

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Introduction Previous studies have shown that hypoxia play an important role in the pathophysiology of endometriosis with increased expression of hypoxia-inducible factor-1alpha (HIF-1α), a key mediator of cellular adaptation to low-oxygenic level. Emerging data have shown increased platelets aggregation in endometriotic lesions and that endometriotic cells and platelets engage cross-talks to facilitate the development of endometriosis. In addition, co-culture of endometriotic stromal cells with activated platelets promotes cellular proliferation, angiogenesis, and the up-regulation of genes that are known to be involved in endometriosis, such as cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF). Platelets activate TGF-β1/Smad3 pathway in endometriotic cells, resulting in epithelial-mesenchymal transition (EMT) and fibroblast-to-myofibroblast transdifferentiation (FMT) in endometriosis. The aim of this study was to see as whether activated platelets can also induce HIF-1α expression and its downstream target genes, such as VEGF, COX-2, and erythropoietin (EPO), in human endometriotic stromal cells (HESCs) and human endometrial stromal cell line (ESCL).

Material/Patients and methods After co-culture of HESCs and ESCL with different treatment medium for 48 hours, we performed analyses to quantify the gene and protein expression of HIF-1α, VEGF, COX-2 and EPO.

Results We show that the gene and protein expression levels of HIF-1α and its target genes were significantly elevated in HESCs or ESCL after co-culture with activated platelets as compared with controls. Neutralization of TGF-β1 through the use of A83-01, a TGF-β1 receptor inhibitor resulted in a significantly abrogated the platelet-induced expression of HIF-1α and its target genes.

Conclusion These results demonstrate that platelets can induce hypoxia in endometriotic lesions, resulting, among other things, in increased angiogenesis. This induction is, in part, through the TGF-β signaling pathway. Considering that hypoxia induces many important downstream genes to regulate the implantation, survival, and maintenance of ectopic endometriotic lesions, our findings highlight the critical role of platelets in the development of endometriosis.

Keywords : Endometriosis; HIF-1α; TGF-β; Platelet
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