# Hypoxia-hindered methylation of PTGIS in endometrial stromal cells accelerates endometriosis progression by inducing CD16 - NK-cell differentiation

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Exp Mol Med. 2022 Jul 4. doi: 10.1038/s12276-022-00793-1. Online ahead of print.

## Abstract

Prostacyclin (PGI2) plays key roles in shaping the immune microenvironment and modulating vasodilation, whereas its contribution to endometriosis (EMs) remains largely unclear. Our study suggested that prostacyclin synthase (PTGIS)-dependent PGI2 signaling was significantly activated in EMs, which was involved in the hypoxic microenvironment of ectopic lesions and deficient methylation status of the PTGIS promoter. Notably, in vitro assays, hypoxia promoted PTGIS expression through DNA methyltransferase 1 (DNMT1)-mediated DNA methylation deficiency in endometrial stromal cells (ESCs); PTGIS overexpression enhanced the adhesive ability of ESCs and led to elevated PGI2 production, and PGI2 triggered CD16- (encoded by FCGR3, Fc fragment of IgG receptor IIIa) natural killer (NK)-cell differentiation through PGI2 receptor (IP, PTGIR) in an ESC/NK-cell coculture system. Our rodent model experiment suggested that treatment with the PGI2 analog iloprost and adoptive transfer of fcgr3 knockout (fcgr3-/-) NK cells aggravated EMs progression and that genetic ablation of ptgis (ptgis-/-) in ectopic lesions and treatment with the PTGIR antagonist RO1138452 partially rescued this outcome. Thus, our findings identified the contribution of PGI2 to EMs progression via enhancement of the adhesive ability of ESCs and inhibition of the activity of NK cells. We hypothesized that PGI2 is a target for EMs intervention and provide a rationale for studying pharmacological PTGIR inhibition and PTGIS genetic depletion therapies as therapeutic strategies for EMs.