Suppression of COUP-TFII by Proinflammatory Cytokines Contributes to the Pathogenesis of Endometriosis

Shih-Chieh Lin¹, Yo-Hua Li², Meng-Hsing Wu³, Yu-Fan Chang¹, Dong-Kee Lee⁴, Sophia Tsai⁴, Ming-Jer Tsai⁴, Shaw-Jenq Tsai¹,²,*

¹ Department of Physiology, Institute of Basic Medical Sciences, National Cheng Kung University, Tainan 70101, Taiwan
² Department of Obstetrics and Gynecology, National Cheng Kung University, Tainan 70101, Taiwan
³ College of Medicine, National Cheng Kung University, Tainan 70101, Taiwan
⁴ Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas 77025, United States of America

seantsai@mail.ncku.edu.tw


Endometriosis is a common gynecological disease in women of reproductive age, and always leads to chronic pelvic pain and infertility. Surgical removal of endometriotic lesions is the gold standard of current treatment regimen; however, about 50% of patients relapse within 5 years after surgery. Therefore, it is critical to study underlying mechanisms responsible for endometriosis formation and find novel strategies against high recurrence rate of endometriosis.

Chronic pelvic inflammation has been observed in patients with endometriosis and is associated with disease severity. Elevated pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and transforming growth factor-β, were found to be elevated in the peritoneal fluid of women with endometriosis; however, the pathological function of these proinflammatory cytokines in endometriosis development remain largely uncharacterized. Herein, we demonstrate that these pro-inflammatory cytokines inhibit the expression of chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII) in endometrial stromal cells. COUP-TFII is a transcriptional repressor that directly binds to the cyclooxygenase-2 (COX-2) promoter in endometrial stromal cells. Thus, loss of COUP-TFII in endometriotic stromal cells results in de-repression of COX-2 and overproduction of prostaglandins, especially prostaglandin E₂ (PGE₂). Because PGE₂ is a master regulator in controlling the pathogenesis of endometriosis, reduced COUP-TFII expression and thus overproduction of PGE₂ by proinflammatory cytokines results in increased endometriotic cell proliferation and severity of endometriosis.

Taken together, we demonstrate that proinflammatory cytokines inhibit COUP-TFII expression, which leads to overexpression of COX-2 and aberrant production of PGE₂. Overproduction of PGE₂ increases angiogenesis and steroidogenesis in endometriotic lesion and reduced phagocytosis of macrophages. As a result, this hastens the development of endometriosis and causes more severe symptoms of patients with endometriosis.