NOVEL INSIGHTS INTO THE PATHOGENESIS OF ENDOMETRIOSIS: ROLE OF SPHINGOSINE 1-PHOSPHATE SIGNALING AXIS

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Endometriosis, an inflammatory disease characterized by the presence of tissue outside the uterus that resembles endometrium, affects ~10% of women and is associated with pelvic pain and infertility. The etiology of endometriosis is unclear but there is increasing evidence that transforming growth factor (TGF)-β plays a major role, being implicated in the development of fibrosis. Nevertheless, the molecular mechanisms implicated in TGF-β action are less clear.S1P is a pleiotropic bioactive sphingolipid involved in the regulation of many pathophysiological functions. It is generated by the phosphorylation of sphingosine catalyzed by sphingosine kinase (SK1 and SK2) whereas the catabolism of S1P is mediated by S1P lyase and by two distinct S1P phosphatase. The majority of S1P effects are mediated by a family of G protein-coupled receptors, S1P1-5. A complex cross-talk between S1P signaling and cytokines has been observed, promoting multiple biological actions such as survival and fibrosis. We demonstrated that the well-known fibrotic action of TGFβ relies on S1P signaling axis in a human cell line of the uterine cervix. Moreover, we provide the first evidence that S1P acts as a pro-fibrotic cue in the same cellular model. In addition, by comparing the expression of genes related to S1P metabolism and signaling between endometriotic lesions and healthy endometrium we demonstrated that S1P metabolism and signaling are profoundly dysregulated in endometriosis. Indeed, in ovarian cysts the enzyme SK1 and its activating protein CIB1 are significantly up-regulated respect to control endometrium. Moreover, S1P1 expression is significantly increased in ovarian cysts, suggesting that endometriosis is characterized by an augmented synthesis of S1P that, following its interaction with S1P1 receptor, may be involved in endometriosis pathogenesis. These findings highlight a crucial role of S1P signaling in endometriosis, opening new perspectives for its phamacological treatment.