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S. Bradbrook/NPG

REPRODUCTIVE IMMUNOLOGY

Evading immunosurveillance in endometriosis

Endometriosis is caused by the deposition and growth of endometrial tissue fragments outside of the uterus. In healthy women, it is thought that ectopic debris that is shed into the peritoneal cavity by retrograde menstruation is cleared by the immune system, whereas, in women with endometriosis, the endometrial tissue fragments must evade immune surveillance. Expression of intracellular oestrogen receptor-β (ERβ) is greatly elevated in endometriotic tissue compared with normal endometrial tissue; however, its role in the pathogenesis of endometriosis remains to be fully determined. Reporting in *Cell*, Han *et al.* show that ERβ interacts with components of the cell death machinery in endometriotic cells to block tumour necrosis factor (TNF)-induced apoptosis and enhances inflammasome-mediated interleukin-1β (IL-1β) production to promote cell adherence and proliferation.

> “elevated ERβ levels in endometriotic tissue disrupt apoptosis complex I, apoptosis complex II and apoptosome formation”

The authors first confirmed that, in mouse endometriotic tissue, the expression and activity of ERβ is greatly increased compared with normal endometria. Loss of ERβ expression decreased ectopic lesion volume, reduced cell proliferation and increased apoptosis in mouse endometriotic tissue. By contrast, overexpression of ERβ increased lesion volume and cell proliferation, and decreased apoptosis.

To understand how ERβ modulates apoptosis and proliferation, the authors determined the cellular proteins with which ERβ interacts, using co-immunoprecipitation. They found that apoptosis signal-regulating kinase 1 (ASK1), serine/threonine kinase receptor-associated protein (STRAP) and 14-3-3 proteins form a complex with ERβ specifically in cells from ectopic lesions. ASK1 is a component of the TNF-induced apoptosis complex I, the formation of which is disrupted by STRAP and 14-3-3 proteins. In addition, ERβ was shown to interact with the endometriotic steroid receptor co-activator 1 (SRC1) isoform and with caspase 8, which is a component of apoptosis complex II, and this interaction inhibited caspase 8 activation. Of note, inhibition of both ERβ and the SRC1 isoform significantly suppressed ectopic lesion growth compared with inhibition of the individual molecules. Further studies showed that the levels of cytochrome *c* and cleaved caspase 9 in ERβ-overexpressing lesions were lower than in control lesions. TNF-induced cytochrome *c* promotes the formation of the apoptosome, in which apoptotic protease-activating factor 1 (APAF1) interacts with caspase 9 to promote its cleavage. Indeed, no APAF1 and caspase 9 interaction was observed in ERβ-overexpressing lesions. Together, these data suggest that elevated ERβ levels in endometriotic tissue disrupt apoptosis complex I, apoptosis complex II and apoptosome formation to protect cells from TNF-induced apoptosis.

Further investigation showed that ERβ also interacts with caspase 1 and NOD-, LRR- and pyrin domain-containing 3 (NLRP3), both of which are components of the inflammasome that mediates mature IL-1β production. Previous studies have shown that IL-1β is involved in the adhesion and proliferation of endometrial cells, and ERβ-deficient cells had reduced levels of active caspase 1 and IL-1β. The importance of NLRP3 in endometriosis pathogenesis was highlighted by the observation that ectopic lesion volume was greatly reduced in NLRP3-deficient mice compared with controls.

Finally, immortalized human endometriotic cells that stably express ERβ were resistant to TNF-induced apoptosis and produced high levels of IL-1β. These human cells also promoted the formation of ectopic lesions in a mouse model of endometriosis compared with control cells. Furthermore, primary human endometriotic cells were shown to express higher levels of ERβ, IL-1β and anti-apoptotic signalling molecules upon TNF stimulation than control endometrial cells.

Together, these data suggest that ERβ protects endometriotic cells from immunosurveillance by inhibiting TNF-induced cell death pathways and promotes ectopic lesion growth by enhancing inflammasome-induced IL-1β production.

Olive Leavy

ORIGINAL RESEARCH PAPER Han, S. J. *et al.* Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. *Cell* **163**, 960–974 (2015)