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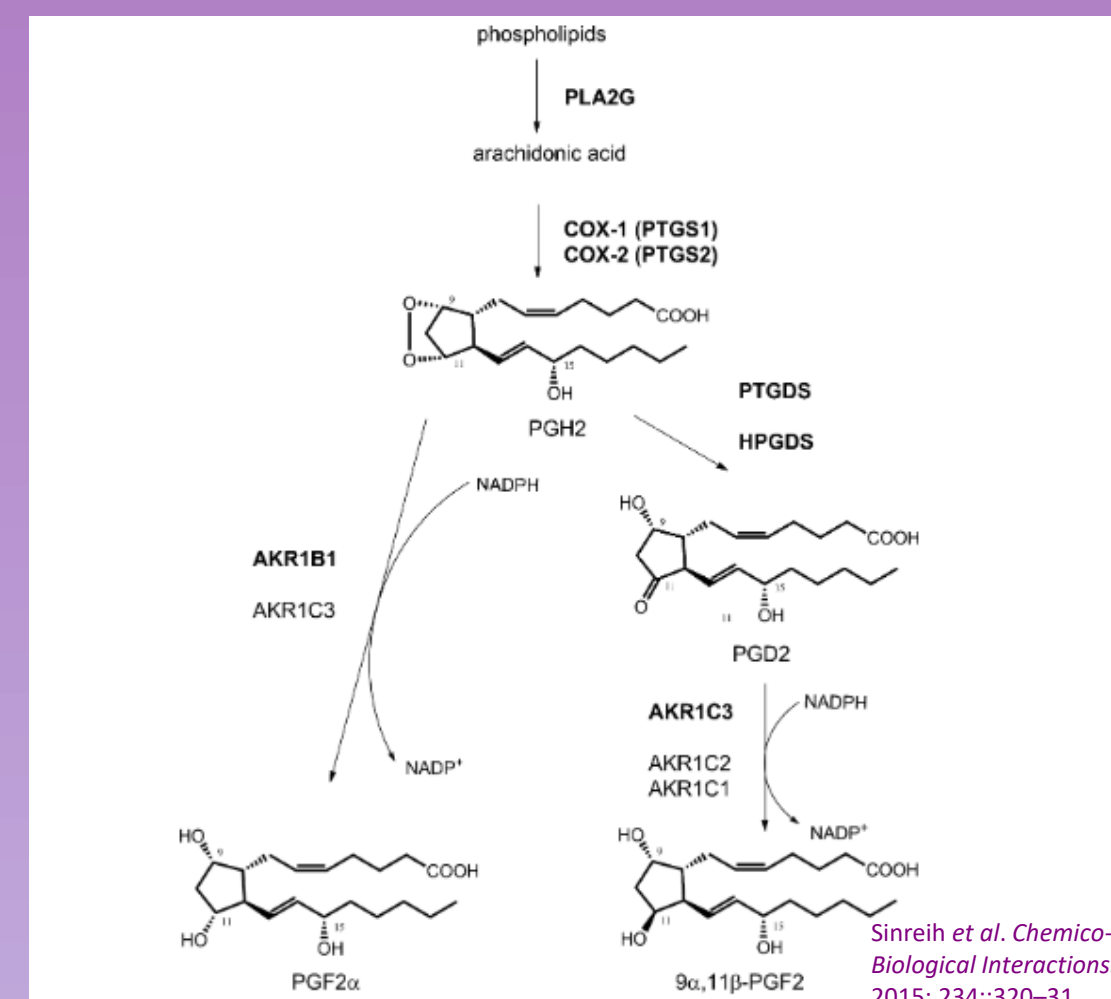
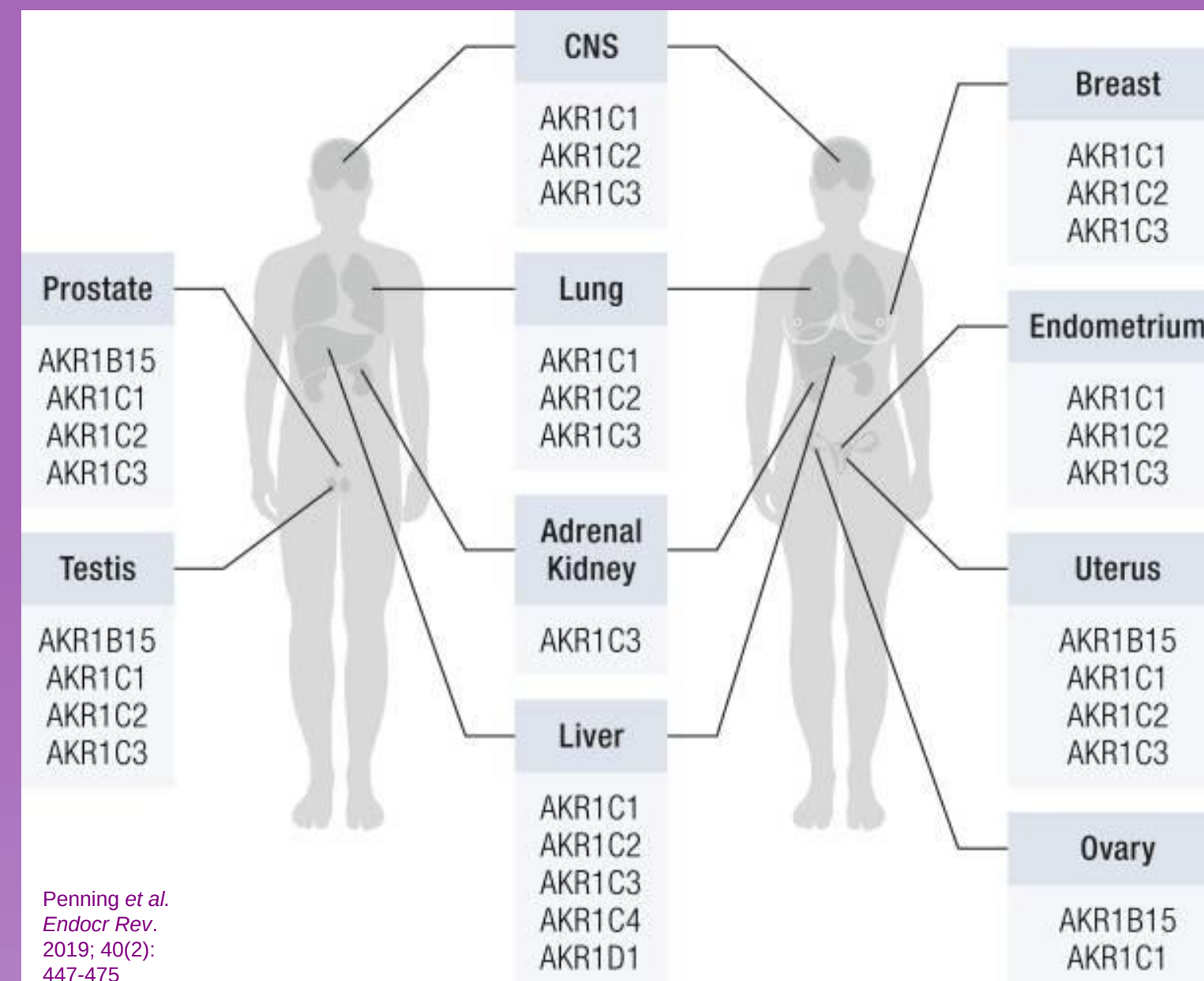
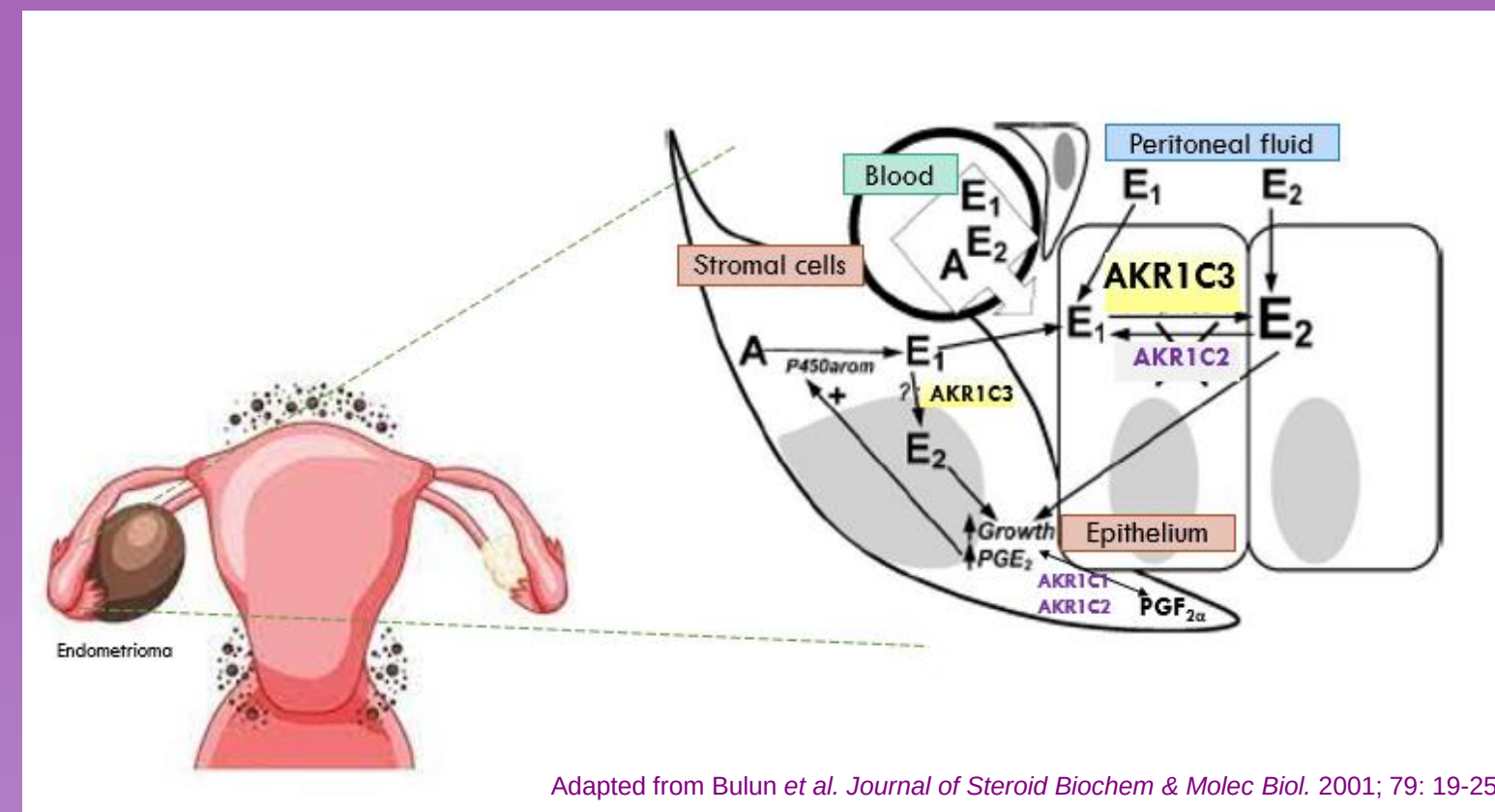
The Problem

- Endometriosis is a chronic inflammatory condition
- It affects 1 in 10 women of reproductive age¹
- Symptoms can be debilitating, detrimental to quality of life and have a huge economic cost²
- Driven by cyclical increases in oestrogen³
- Surgery can be complex and associated with risk of complications
- Symptomatic control with analgesia does not alter the disease process
- Hormonal treatments limit options for fertility

A more effective and acceptable treatment is drastically needed

Aldo-Keto Reductase Enzymes

- Superfamily of >190 members⁴
- 15 exist in humans⁴
- Found all over the body

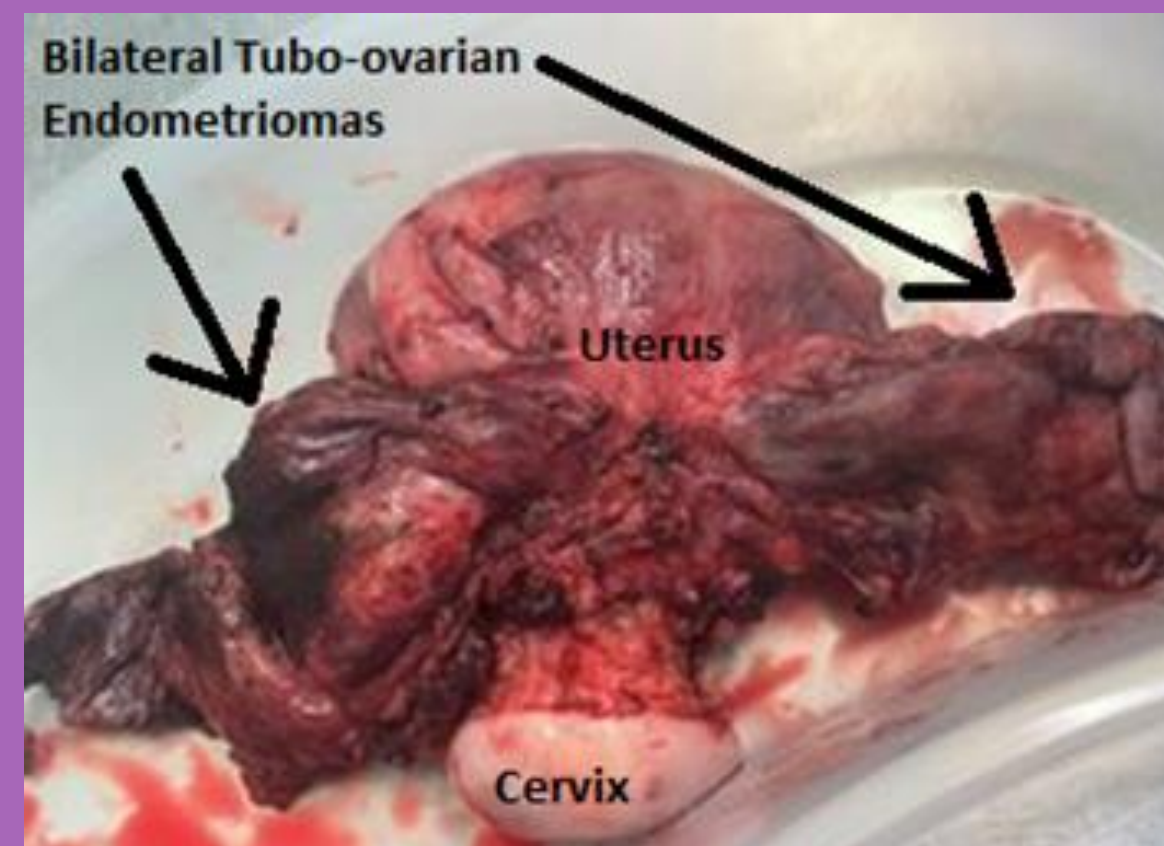


- Important in steroid hormone metabolism and prostaglandin synthesis^{4, 5}
- Aldo-keto reductase (AKR)1C1, AKR1C2, AKR1C3, AKR1B1 & AKR1B10 all have a potential role in endometriosis⁶
- The AKRs also have paracrine action within the endometriotic lesions themselves⁷
- AKR1C3 converts oestrone (E1 – inactive) to its active form oestradiol (E2), which further potentiates proliferation⁵
- All 5 play a role in Prostaglandin F_{2α} synthesis, with AKR1B1 and AKR1C3 predominating⁴

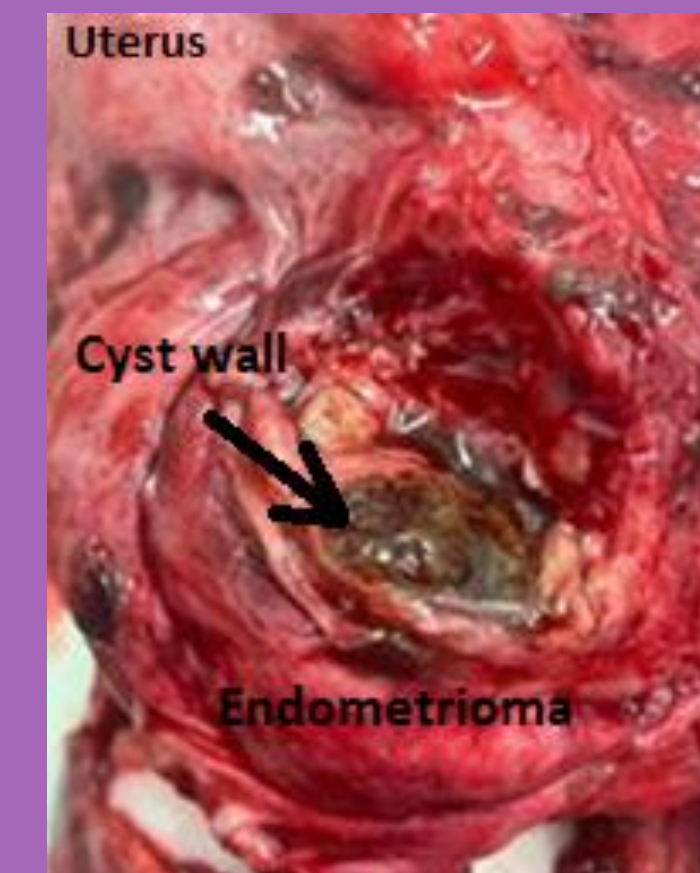
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RNA Extraction from Human Tissue Samples



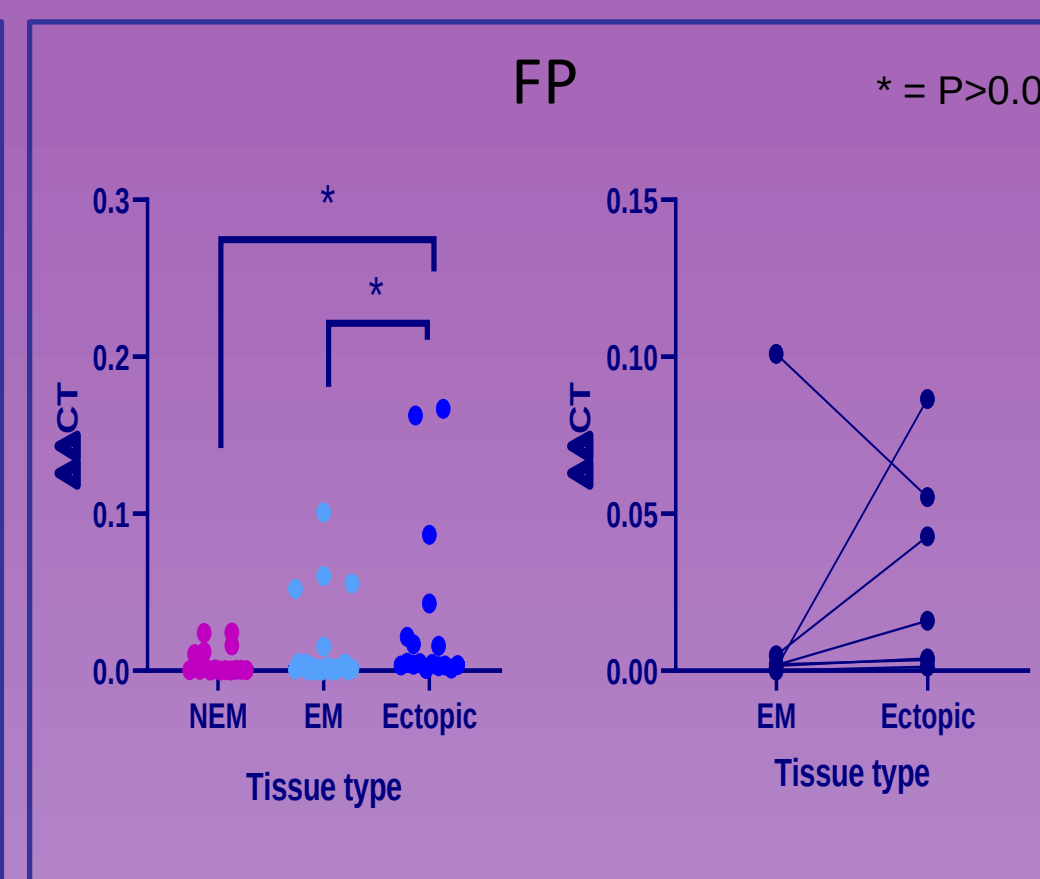
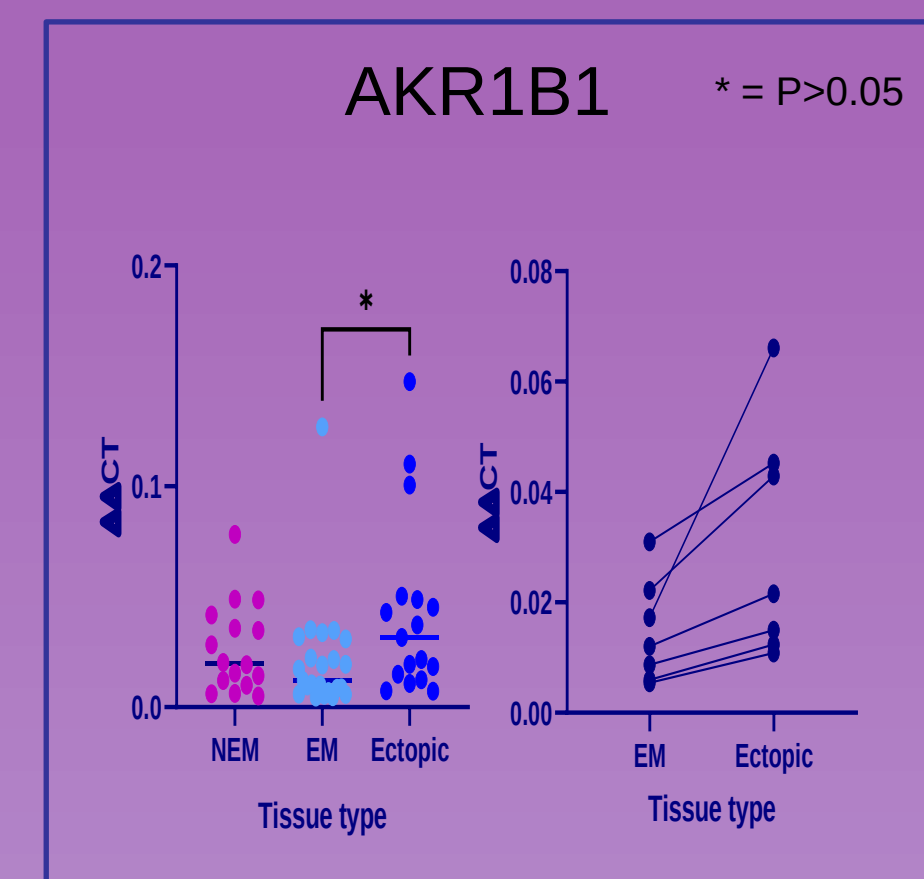
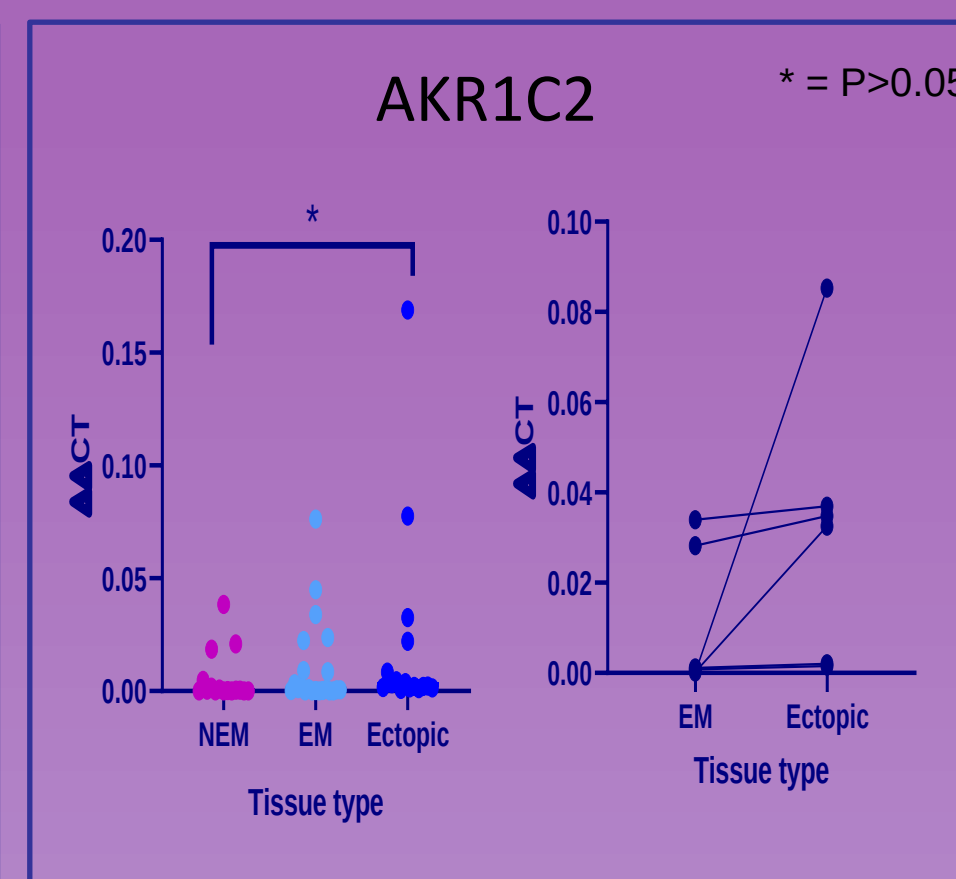
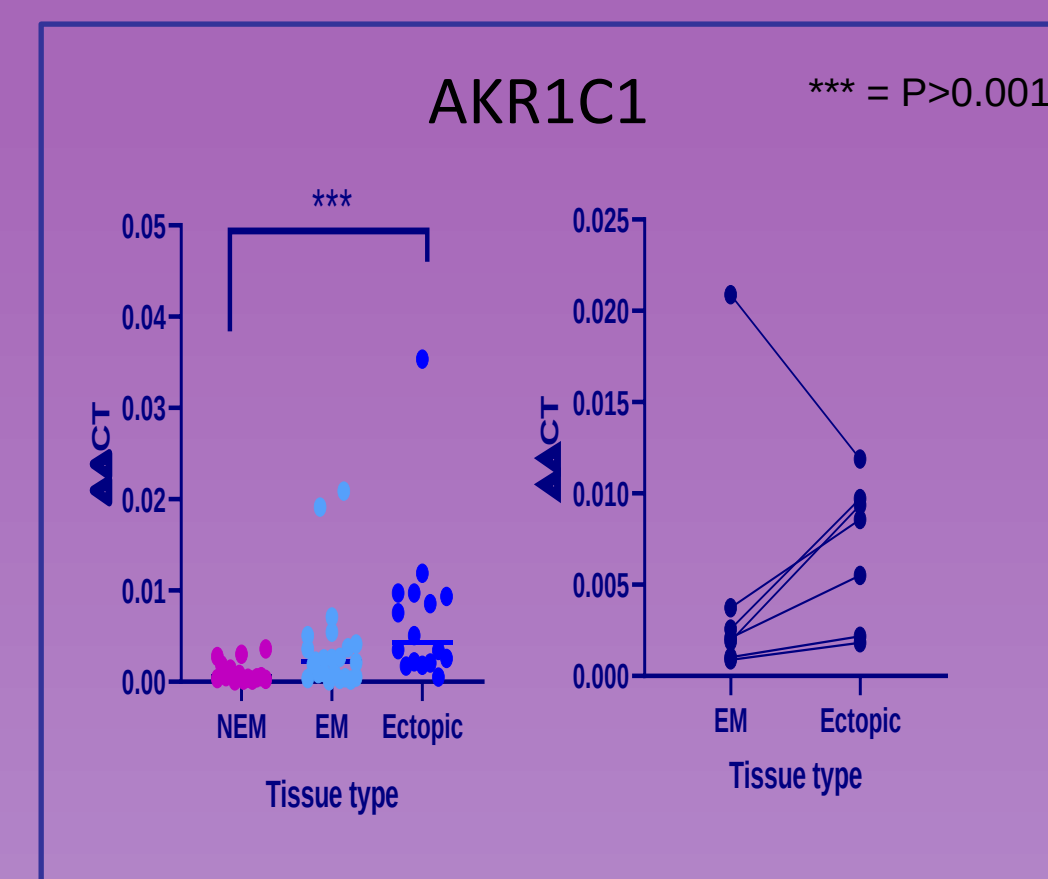
- Tissue samples were obtained from consenting patients undergoing gynaecological surgery
- 16 patients did not have a diagnosis of endometriosis
- 23 were diagnosed with endometriosis (confirmed histologically)
- Of these 23, 17 had endometriomas
- Biopsies were taken from eutopic endometrium, as well as tissue from endometriomas
- The diagnosis of endometrioma is less subjective than peritoneal endometriosis, and the samples obtained were larger than peritoneal deposits, so tissue from endometriomas was used.
- RNA extraction and PCR were undertaken



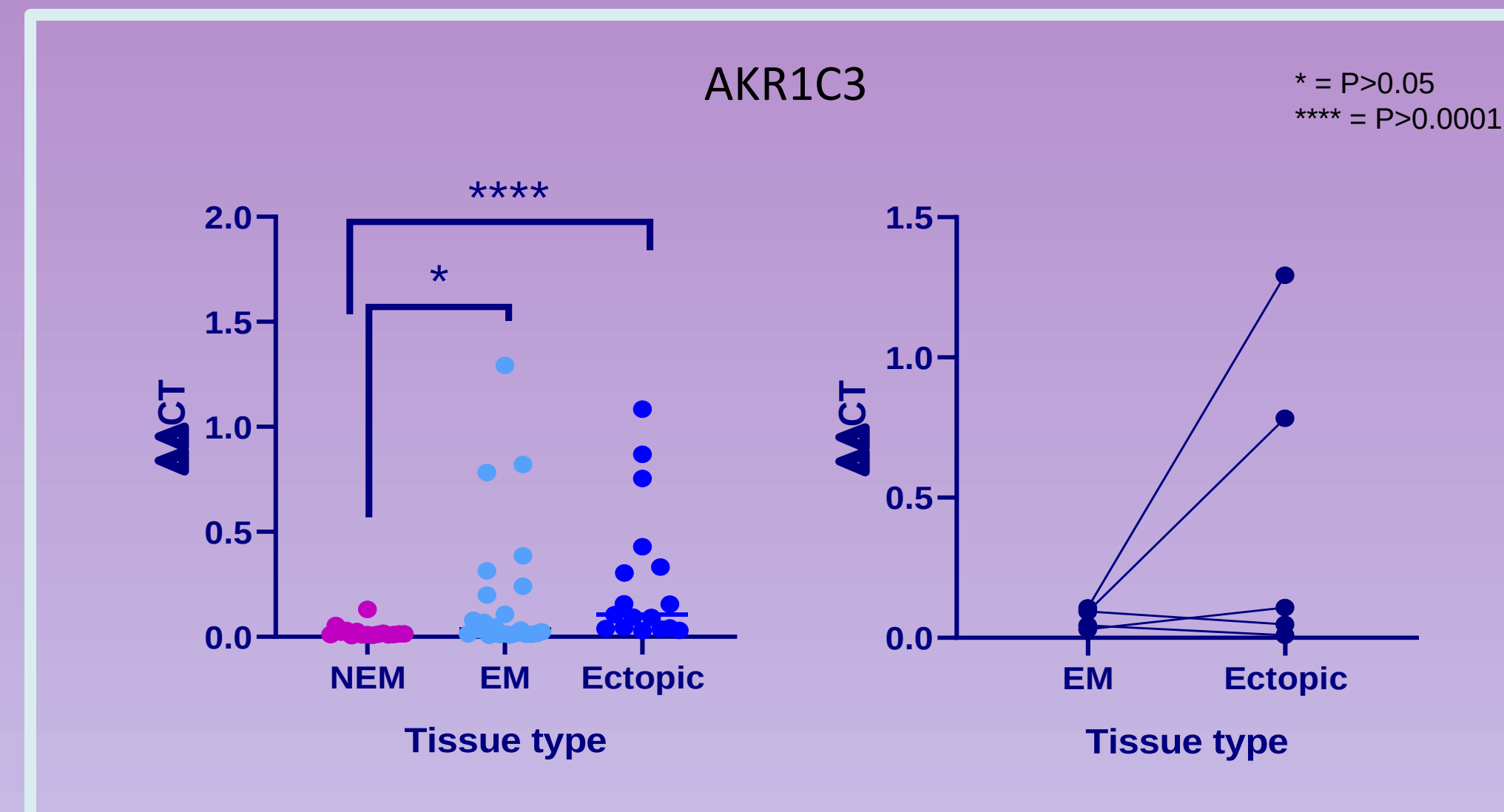
Results

Graphs Demonstrate Expression of AKRs and FP in:

- Eutopic endometrium of patients without endometriosis (NEM),
- Eutopic endometrium of patients with endometriosis (EM) and
- Ectopic endometrium/tissue from endometriomas (Ectopic)



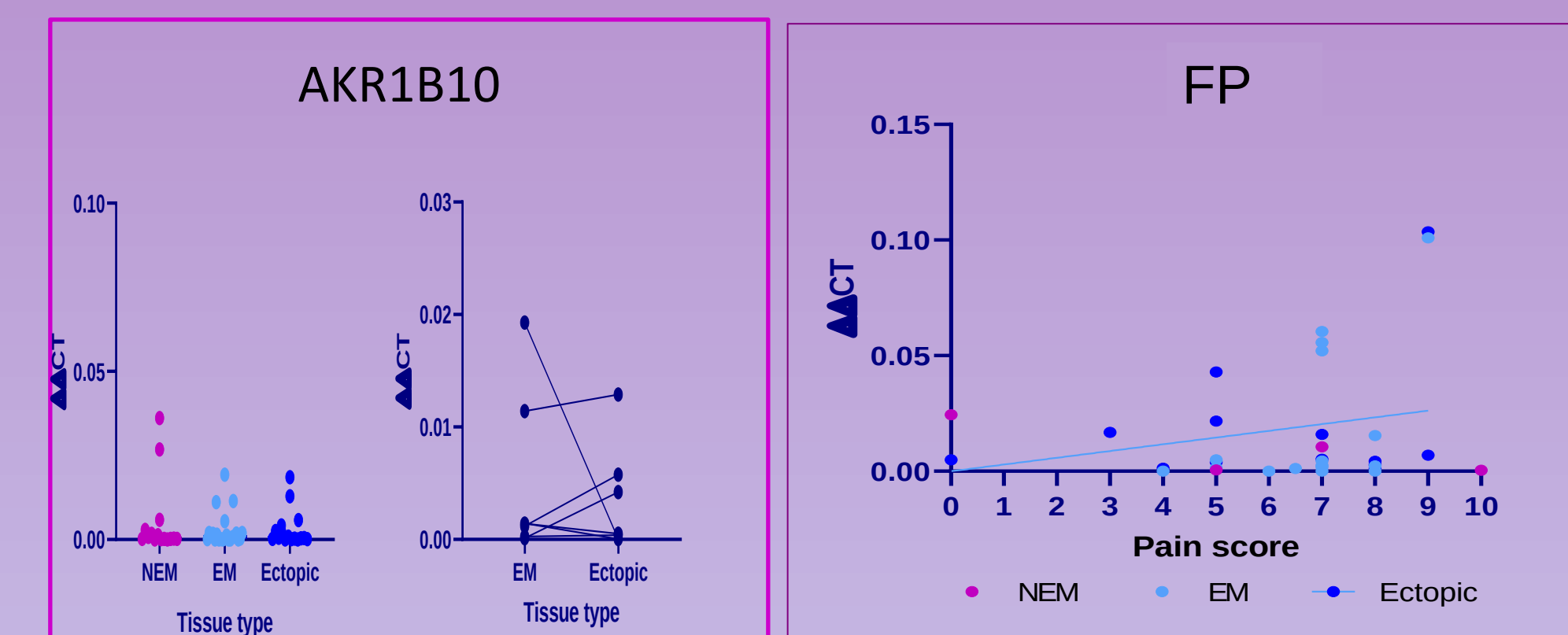
AKR1C1 & AKR1C2 expression was increased in ectopic endometriotic lesions, when compared to eutopic endometrium of patients without endometriosis



Significantly increased expression of AKR1C3 was observed between eutopic endometrium of those without endometriosis and ectopic lesions. Increased AKR1C3 was also demonstrated in eutopic endometrium of those with endometriosis, when compared to those without

Also demonstrated, is correlation between paired samples (eutopic endometrium vs ectopic tissue from the same patient)

AKR1B1 and FP receptor expression also increased in ectopic tissues compared to eutopic endometrium from women with and without endometriosis

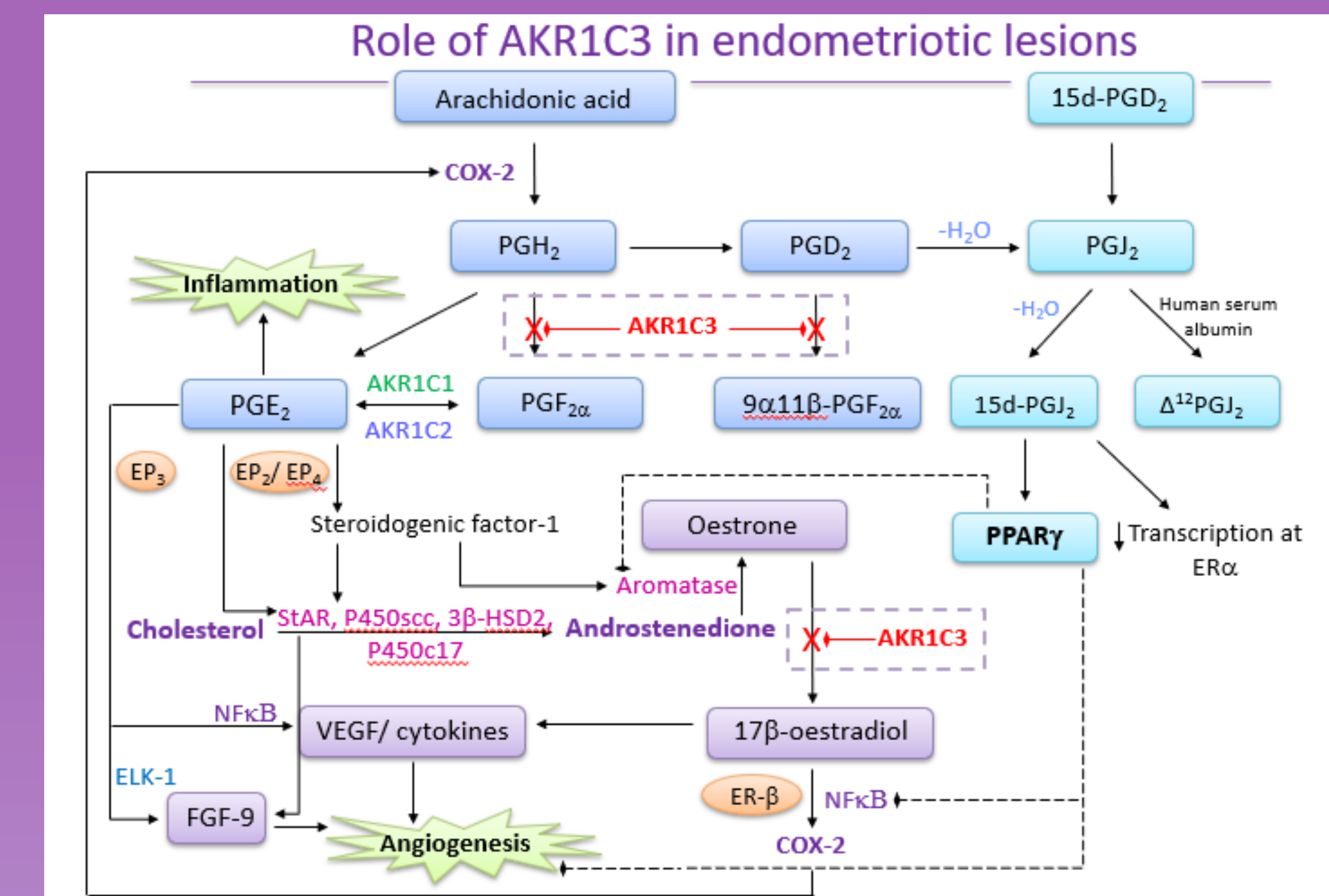


AKR1B10 transcripts at limit of detection - no significant differences

Expression of FP within the endometrium of women with endometriosis correlated to pre-operative average daily pain score (p<0.05)

Conclusions & Further Research

- We have demonstrated that expression of four of the AKRs are elevated in patients with endometriosis
- AKR1C3 was the most abundant AKR enzyme and expression was elevated in endometriosis, indicating its potential as a therapeutic target
- FP receptor expression within the eutopic endometrium correlated with higher pain scores in women with endometriosis.
- Possible causes of this include: PGF_{2α} causing uterine hypercontractility and uterine ischemia, as well as increased sensitisation of nerve fibres, fibroblast proliferation, cell migration and collagen deposition



- Inhibition of AKR1C3 may disrupt the self-perpetuating micro-environment of endometriosis, stopping proliferation, inflammation and subsequent adhesive disease
- This may also enable targeted, locally delivered drug therapy that would not interfere with the menstrual cycle. Therefore, providing a more acceptable treatment option.
- We are yet to examine peritoneal lesions, normal peritoneum, deep/rectovaginal endometriotic nodules and adenomyotic endometrium, but are interested to ascertain expression of the AKRs within these tissues
- We intend to measure PGF_{2α} in patients with and without endometriosis, and ultimately determine if an AKR1C3 inhibitor reduces PGF_{2α} and oestradiol

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