Endometriosis and Ovarian Cancer: An Inflammatory Phenotype

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I have no meaningful conflicts of interest to declare
Background

• Ovarian cancer is the most common cause of death of all gynecological tumors\textsuperscript{1}
  – 5\textsuperscript{th} most prevalent cause of cancer-related death overall\textsuperscript{1}
  – Epithelial ovarian cancer subtypes \textsuperscript{4}:
    • Mucinous
    • Endometrioid
    • Clear Cell
    • High grade serous
    • Low grade serous
Background

• Endometriosis affects 5 to 15% of the population
  – Defined by presence of endometriotic glands and stroma found outside of the uterus
  – Driven by estrogen-dependence and progesterone resistance

5 - References

6 - References
Background

- Endometriosis shares features with malignancy
- Evolution of malignant endometriosis most commonly associated with endometrioid, mucinous, low-grade serous, and clear cell subtypes\textsuperscript{5-9}
- Genetic changes linked to both diseases:
  - P53, KRAS, PI3KCA, MYC, SIRT1, and AT-rich interactive domain 1A (ARID1A)\textsuperscript{8-11}
Background

- KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)
  - Important in the RAS/MAPK pathway\textsuperscript{12,13}
  - KRAS mutations found in endometrioid, mucinous, low-grade serous, and clear cell carcinomas\textsuperscript{12}

Berg M, Soreide K. *Discov Med*, 2012. 14(76) 207-214,
Background

• SIRT1 (Sirtuin-1) plays critical role in regulating cell division, aging, and metabolism\textsuperscript{11}
  – Dual function as tumor suppressor and oncogene\textsuperscript{16}:
  – SIRT1 over-expressed in endometriosis and co-expressed with BCL6\textsuperscript{17}
  – In one study, SIRT1 higher in malignant compared to benign, but predicted overall favorable prognosis in ovarian cancer\textsuperscript{19}

Background

- ARID1A (AT-rich interactive domain 1A)
  - Encodes BAF250a\(^{26}\)
  - Mutation of ARID1A in 50% clear cell and 30% of endometrioid ovarian cancers\(^{27}\)
  - ARID1A prevents repression of RelA recruitment of cytokines\(^{28}\)
  - Reduced ARID1A in endometrium of women with endometriosis\(^{24}\)

Kim et al., Cell reports 2016;17:275-88
Objective

To evaluate the association between KRAS, SIRT1, and ARID1A expression in women with endometriosis and endometriosis-associated ovarian cancers in order to better understand their contribution to the pathogenesis from benign disease to malignancy
HYPOTHESES

• ARID1A and SIRT1 are specifically associated with endometriosis and ovarian cancer associated with endometriosis

• Imbalance between SIRT1 and KRAS leads to progesterone resistance and altered ARID1A expression

• ARID1A is reduced in endometriosis and endometriosis-associated ovarian cancers

GOALS

• Compare KRAS in normal cycle, endometriosis, and ovarian cancers with and without endometriosis

• Compare SIRT1 in normal cycle, endometriosis, and ovarian cancers with and without endometriosis

• Examine ARID1A in normal cycle, endometriosis, and ovarian cancers with and without endometriosis
Methods
Methods

• **Design:**
  – Immunohistochemistry of KRAS, SIRT1, and ARID1A in samples of uterine sections and ovarian cancer tissue obtained from biorepositories of women with and without endometriosis
  
    • Compare normal cycle, endometriosis, and ovarian cancers with and without endometriosis
Methods

• **Participants:**
  – Inclusion criteria:
    • Regularly cycling women between 18-50 years undergoing hysterectomy for benign indications at GHS, UNC, Michigan State
  – Exclusion criteria:
    • IUD or hormonal therapies 3 months preceding surgery
Methods

• **Outcomes:**
  – Primary:
    • Expression of KRAS, SIRT1, and ARID1A graded by H-score
  – Secondary:
    • Correlation of KRAS and SIRT1
    • ARID1A expression during normal cycle
Statistical Analysis

• Performed using GraphPad:
  – One-way ANOVA analysis
  – Tukey’s post hoc and t-tests
• $p < 0.05$
Results
Results

Cytoplasmic KRAS expression

Figure 1.

Results represent mean ± SEM

* $p<0.05$

** $p<0.01$

*** $p<0.001$
Results

Nuclear and Cytoplasmic SIRT1 expression

Figure 2.
Results

Correlation between KRAS and SIRT1 in ovarian cancer with endometrioma

Figure 3.
Results

Correlation between KRAS and SIRT1 in ovarian cancer without endometriosis

Figure 4.

Correlation Coefficient = 0.5481
p = 0.0007

Correlation Coefficient = 0.9112
p < 0.0001
ARID1A expression in endometrium of normal women

Results

$p = 0.339$
Results

ARID1A expression

Results represent mean ± SEM

*  $p<0.05$

** $p<0.01$

*** $p<0.001$
Results

ARID1A expression

B

Eutopic Endometrium

Control
Endometriosis

Ovarian Cancer

Ovarian Cancer
Endometrioma

Ovarian Cancer with endometriosis

Ovarian Cancer with endometriosis

25μm

25μm

25μm

25μm

25μm
Discussion
Discussion

• KRAS is significantly increased in women with endometriosis and ovarian cancer
  – Greatest in actual ovarian cancer tissue in patients with both diseases
Discussion

• SIRT1 is overexpressed in the nucleus of women with endometriosis and endometriosis-associated ovarian cancers
  – No significant difference compared to controls in women without endometriosis

• Cytoplasmic SIRT1 is high in women with ovarian cancer (with and without endometriosis)

• Positive correlation between KRAS and nuclear SIRT1 in patients with endometriosis-associated ovarian cancer
Discussion

• Association between ARID1A in endometriosis-associated ovarian cancers not previously investigated
• ARID1A decreased in patients with endometriosis
• ARID1A uniquely decreased in patients with endometriosis-associated ovarian cancer compared to those with other ovarian cancers.
Conclusion

• Endometriosis-associated ovarian cancers have a unique phenotype compared to other ovarian cancers
• Nuclear SIRT1 is elevated specifically in endometriosis and endometriosis-associated ovarian cancers
• ARID1A is specifically reduced in ovarian cancers associated with endometriosis compared to other ovarian cancers
• Inflammatory changes associated with endometriosis, SIRT1, and ARID1A provide new targets for therapy for this type of cancer
Future Directions

• Investigation of local and systemic proinflammatory cytokines in women with endometriosis-associated ovarian cancers
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References


