
بسم الله الرحمن الرحيم

The Molecular Mechanism of Endometriosis Associated Ovarian Cancer Development

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Endometriosis & Endometriosis associated ovarian cancer

- Numerous epidemiological and histopathological studies support the notion that clear cell and endometrioid carcinomas derive from ovarian endometriosis. Accordingly, these histologic types are referred to as “endometriosis-associated ovarian cancer” (EAOC).

- Also the normal endometrium is considered the origin of endometriosis through retrograde menstruation.

- To provide evidence for a link between the uterine endometrium and Cancers through endometriosis, *Yachida et al* performed whole-exome sequencing of the normal uterine endometrium, endometriosis, and cancer in a CCC patient.

- Numerous somatic mutations, including cancer-associated mutations were recognized among the epithelium from the uterine endometrium, endometriotic lesions distant from and adjacent to the carcinoma, and the carcinoma.

Yachida et al,. Cancers,. 2021

Genetic alterations commonly found in endometrium, endometriosis, and EAOC

Table 1. Previous report of gene alteration in endometrium, endometriosis, endometriosis-associated ovarian cancer, and endometrial carcinoma.

Gene	Function	Specimen				
		Endometrium [48,51,52,103]	Endometriosis [47,48,103–105]	OCCC [76,78,99,100,103,106–114]	OEC [100,103,110]	TCGA Endometrial Carcinoma [60]
PIK3CA	PI3K/Akt/mTOR pathway	•	•	•	•	•
PTEN	PI3K/Akt/mTOR pathway	•	•	•	•	•
ERBB2	PI3K/Akt/mTOR pathway	•	•	•		•
PIK3R1	PI3K/Akt/mTOR pathway	•		•	•	•
KRAS	Ras/MAPK pathway	•	•	•	•	•
NF1	Ras/MAPK pathway	•		•	•	
ARID1A	SWI/SNF complex		•	•	•	•
PPP2R1A	Serine/threonine-protein phosphatase	•	•	•		•
MLH1	Mismatch repair protein	•	•	•		•
CTNNB1	Wnt/β-catenin signaling pathway		•	•		•
KMT2D	Histone methyltransferase	•		•		
FBXW7	Ubiquitin ligase	•			•	•

OCCC: Ovarian clear cell carcinoma, OEC: Ovarian endometrioid carcinoma, TCGA: The Cancer Genome Atlas.

Murakami et al,. Cancers,. 2021

ARID1A and PTEN mutation plays an important role in oncogenesis

- Cancer-associated gene mutations are identified in both endometriosis and normal endometrium (ex. KRAS, PIK3CA). This finding support Dr. Sampson's retrograde menstruation hypothesis, whereby endometriosis derives from menstrual dissemination of endometrial tissue into the peritoneal cavity at the genomic level.

- Scientists used next-generation sequencing technology to identify mutation profiles for CCC and concurrent endometriosis and found shared ARID1A and PIK3CA mutations leading to increased cell proliferation and inhibition of apoptosis.

- These results suggested that ARID1A and PTEN mutation plays an important role in oncogenesis and occurred in the early stage of carcinogenesis.

- Not only inactivation of tumor suppressor genes (PTEN, ARID1A) but also oncogene mutations (cKit, HIF) is needed for malignant transformation.

Yachida et al,. Cancers,. 2021

Molecular mechanism of EAOC development from endometriosis

Hypothesis 1:

- ARID1A loss-of-function mutation accompanied by a loss of ARID1A protein expression is considered one of the most important driver events in endometriosis-associated ovarian cancer

- Yachida *et al* revealed that not only 70 endometriosis samples without ARID1A mutations but also eight endometriosis samples with ARID1A loss-of-function mutations retained ARID1A protein expression

- clear cell carcinoma samples which harbor multiple ARID1A loss-of-function mutations or both a single ARID1A loss-of-function mutation and ARID1A allelic imbalance lost ARID1A protein expression

- These results suggest that a single ARID1A loss-of-function mutation is insufficient for ARID1A loss in ovarian endometriosis and some clear cell carcinoma. Further driver events may be needed for the malignant transformation of ovarian endometriosis with ARID1A loss-of-function mutations.

Yachida et al,. Cancers,. 2021
Yachida et al,. Sci Rep,. 2020

Malignant transformation model of endometriosis focusing on ARID1A alteration

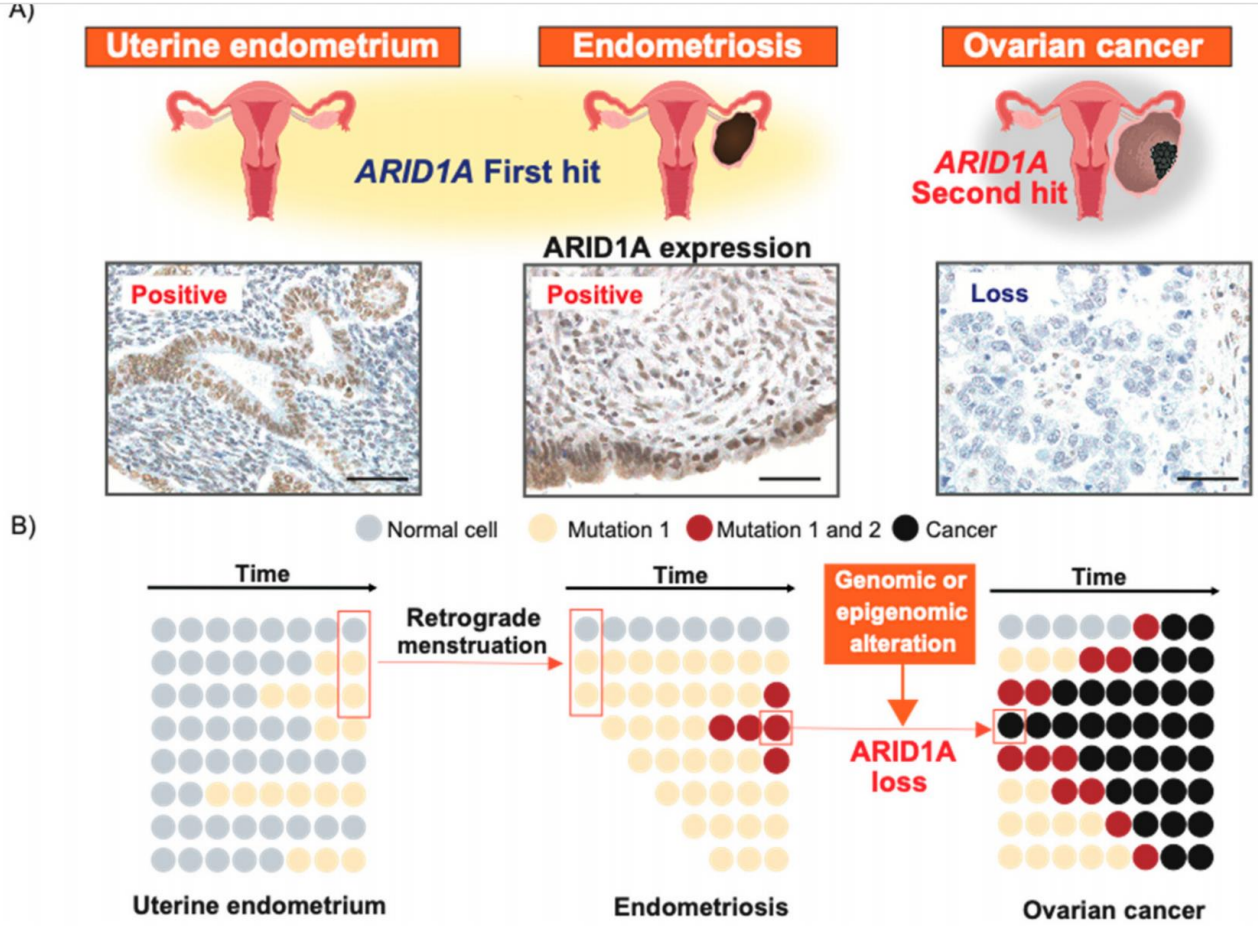


Figure 2. Molecular mechanism of EAOC development from uterine endometrium via endometriosis focused on *ARID1A*. (**A**) The second hit model of *ARID1A* in EAOC development from uterine endometrium via endometriosis. (**B**) The model that explain the process of *ARID1A* mutant cell progression for the development of EAOC.

Yachida et al,. Cancers,. 2021

Molecular mechanism of EAOC development from endometriosis

Hypothesis 2:

- Almost all reported cases of “malignant transformation of ECs” might be “cancer from the beginning.

- The reflux of eutopic endometrial glandular epithelial cells through the fallopian tube might be involved in the development of EAOC, and not through the endometriotic lesions gradually turning into cancer.

- Endometriosis is much more common than EAOC because its mutations are often insufficient as initiators for ovarian cancer. Nonetheless, epithelial cells with sufficient gene mutations, when engrafted in the ovaries, cause carcinogenesis through the effect of the cancer-promoting ovarian microenvironment (defect in the ovarian surface caused by ovulation and cystectomy).

- Finally cells with an initiator mutation may not always cause carcinogenesis.

Murakami et al,. Cancers,. 2021

“Cancer from the beginning” model of EAOC

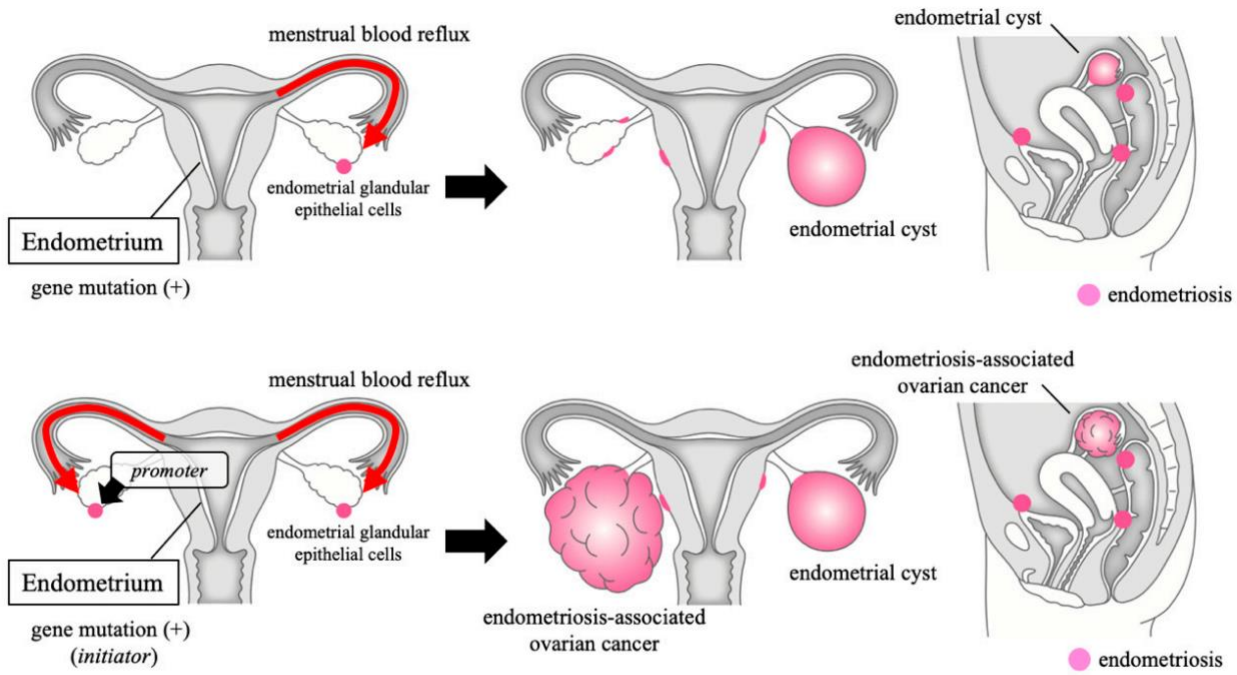


Figure 2. Mechanism of endometriosis-associated ovarian cancer carcinogenesis. Carcinogenesis requires an initiator and a promoter. Gene mutations occur frequently in endometrial glandular epithelial cells, but its mutations are often insufficient as initiators. Nonetheless, endometrial glandular epithelial cells with sufficient gene mutations cause carcinogenesis through the effect of the promoter. If they survive in the contralateral ovary or outside the ovary, they may not cause carcinogenesis, and such cells become endometriosis. This figure was made by modifying a figure from Clinical Gynecology and Obstetrics 2020 [69].

Murakami et al,. Cancers,. 2021

The evidence behind “Cancer from the beginning” model of EAOC

- If ECs are the origin of ovarian cancer, cystectomy should be able to prevent ovarian cancer. However, it was reported that ovarian cancer sometimes occurs in the ipsilateral ovary following cystectomy

- The risk of developing EAOC was reduced with hysterectomy rather than cystectomy of ECs.

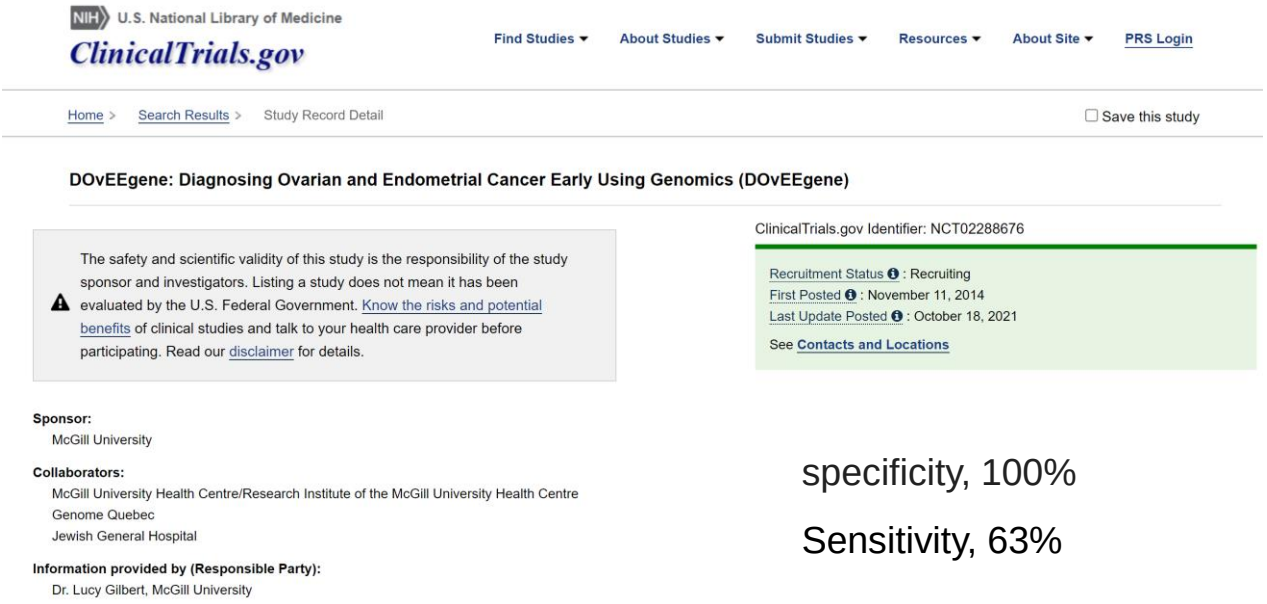
- There is no evidence that EAOC is more likely to develop in older women These data contradict the hypothesis that prolonged exposure to the contents of Ecs leads to DNA damage and increases carcinogenesis

Murakami et al,. Cancers,. 2021

Early endometriosis associated ovarian cancer detection using mutation-based diagnostics PapSEEK

Recent studies have proposed mutation analyses in endocervical or preferably intrauterine cell samples for a potential early detection of endometrial and ovarian cancer.

These DNA-tagging technologies have been shown to be capable of identifying small amount of cancer DNA among thousands of normal cells, the proverbial needle in a haystack.



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DOvEEgene: Diagnosing Ovarian and Endometrial Cancer Early Using Genomics (DOvEEgene)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02288676

Recruitment Status : Recruiting
First Posted : November 11, 2014
Last Update Posted : October 18, 2021

See Contacts and Locations

Sponsor:
McGill University

Collaborators:
McGill University Health Centre/Research Institute of the McGill University Health Centre
Genome Quebec
Jewish General Hospital

Information provided by (Responsible Party):
Dr. Lucy Gilbert, McGill University

specificity, 100%

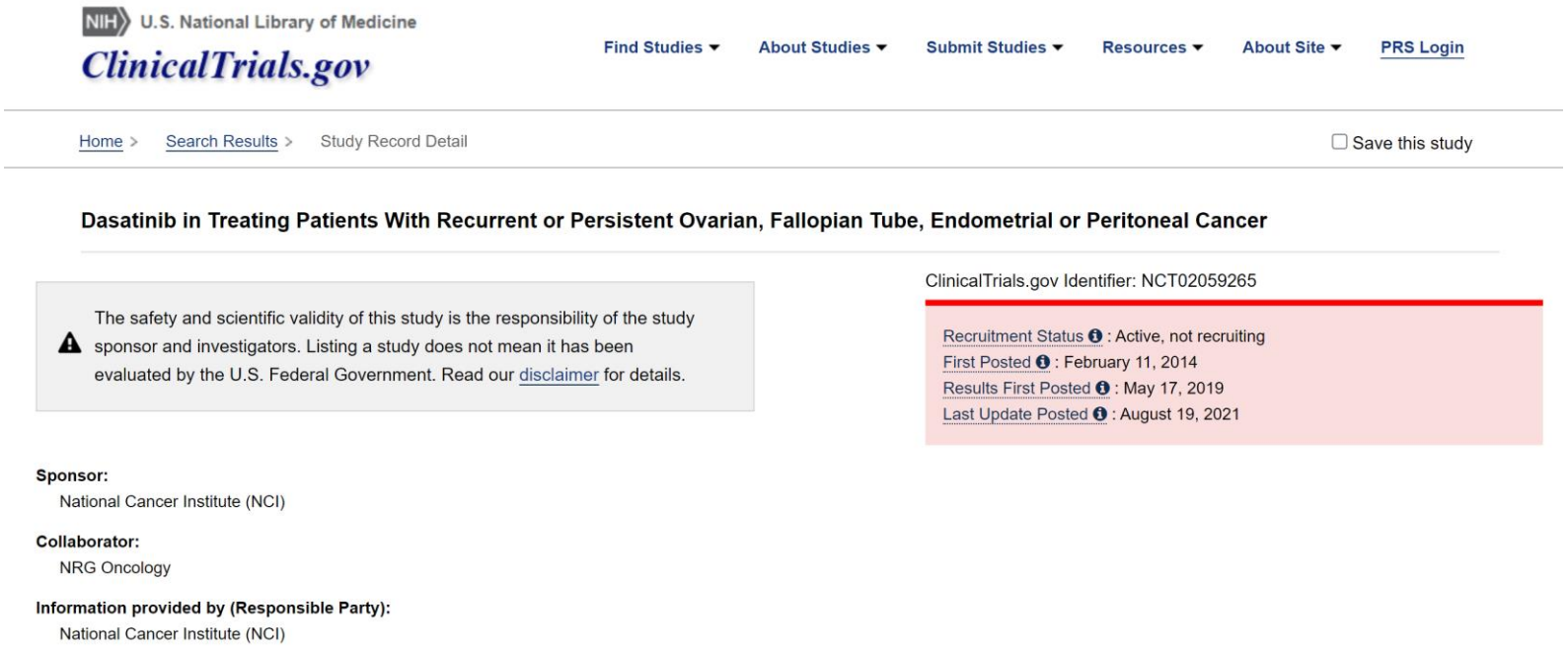
Sensitivity, 63%

If we can accurately and noninvasively diagnose whether a tumor is EC or EAOC, we can avoid overdiagnosis and overtreatment resulting from concerns regarding the malignant transformation of ECs.

Samartzis *et al*,. Ann Transl Med ,. 2020

Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib

Synthetic lethality is defined as a type of genetic interaction where the combination of two genetic events results in cell death or death of an organism.



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Dasatinib in Treating Patients With Recurrent or Persistent Ovarian, Fallopian Tube, Endometrial or Peritoneal Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02059265

Recruitment Status : Active, not recruiting
First Posted : February 11, 2014
Results First Posted : May 17, 2019
Last Update Posted : August 19, 2021

Sponsor:
National Cancer Institute (NCI)

Collaborator:
NRG Oncology

Information provided by (Responsible Party):
National Cancer Institute (NCI)

Dasatinib induced cell cycle arrest in G1 and caspase activity in *ARID1A*-mutant tumor cells.

Miller *et al*,. Mol Cancer Ther,. 2016


Thank you

Adult multipotent stem cells/progenitors may contain a subpopulation of cells with a cancer-associated gene signature

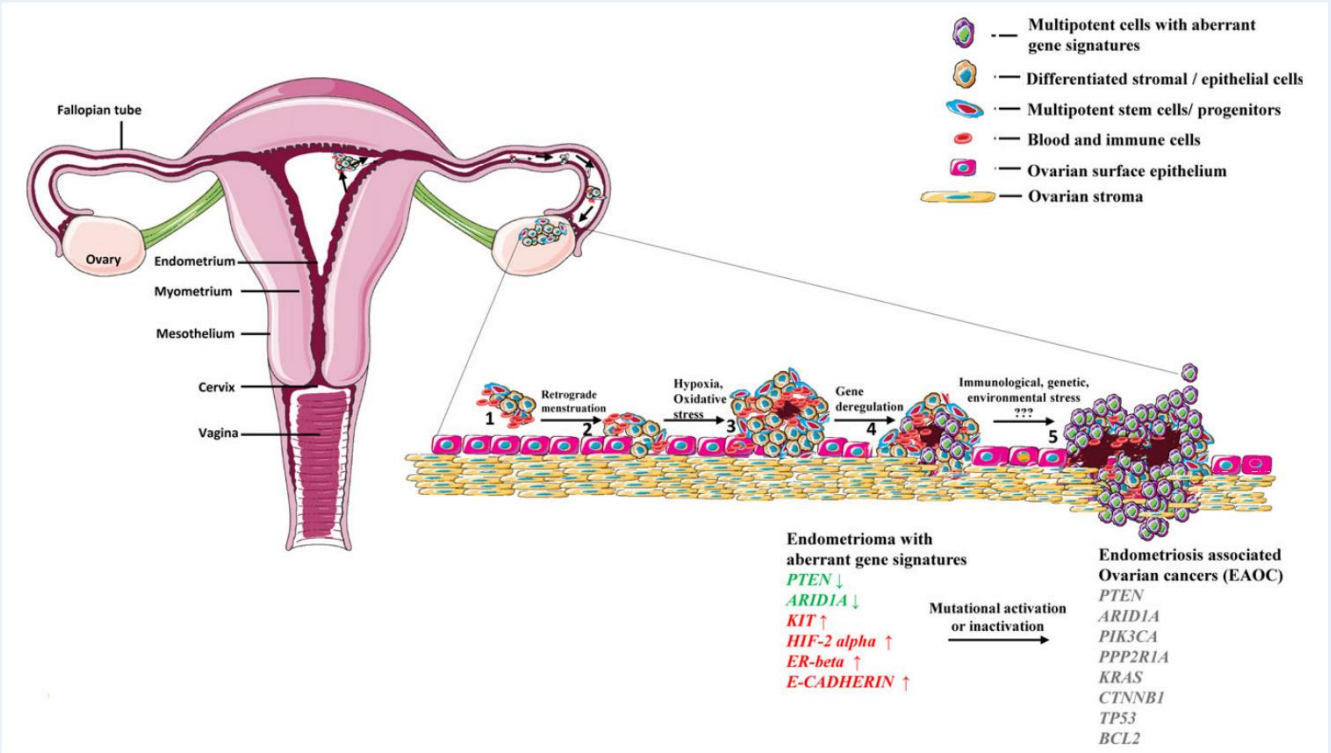

Figure 6 Hypothesis for the development of endometriosis-associated ovarian cancers (EAOC). (1) Initiation: Endometrial differentiated epithelial/stromal cells, multipotent stem cells/progenitors (SC^+) along with red blood cells and immune cells are shed into the peritoneal cavity during menstruation. (2) The cells attach onto the ovaries and form endometrioma. (3) SC^+ in endometrioma (EndoSC) may remain quiescent for several years. Repeated menstrual cycles lead to the accumulation of cell toxic factors including reactive oxygen species, inflammatory cytokines and hypoxia inducing factors; the cells in endometrioma are subjected to mutational stress. (4) As a consequence, EndoSC may undergo gene dysregulation leading to aberrant cellular phenotype forming EAOC precursor lesions. Aberrant expression may include elevated activity of cancer-associated genes (e.g. *KIT*, *HIF2α* and *E-cadherin*), altered *ER-β/ER-α* ratio and downregulation of tumour suppressor genes (*PTEN* and *ARID1A*). (5) Gene dysregulation within EndoSC may create a favourable peritoneal environment to directly or indirectly support the accumulation of several stochastic mutations causing inactivation of tumour suppressor genes *PTEN*, *TP53* and *ARID1A*, and activation of oncogenes *KRAS*, *CTNNB1* and *PIK3CA*, collectively leading to the development of EAOC. Genes marked in red and green were respectively upregulated and downregulated on comparing high and low-expression variability subgroups in this study. Genes marked in grey were previously identified cancer driver gene mutations causing EAOC.

Ponandai-Srinivasan *et al*,. Human Reproduction,. 2018