Endometriosis-related ovarian neoplasm

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Photo courtesy: Endo Found USA

Disclosure Information

AACR Advances in Ovarian Cancer Research
Ieming Shih

Financial relationships that is relevant to this presentation:
Gilead Science

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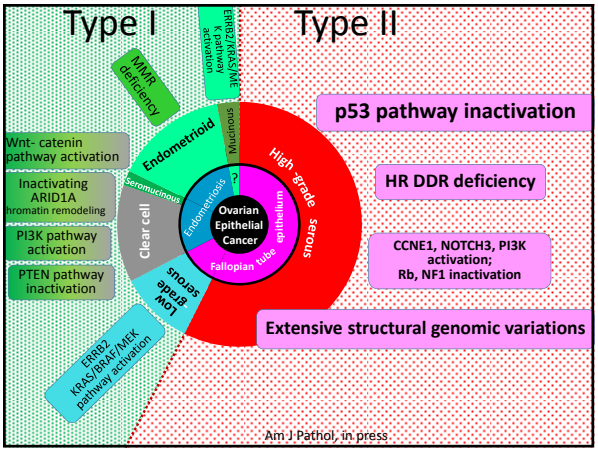
- and -

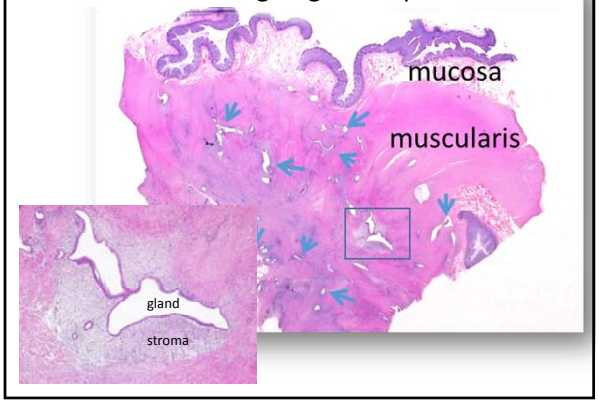
I will **not** discuss off label use and/or investigational use in my presentation.

Why is important to study ERON?

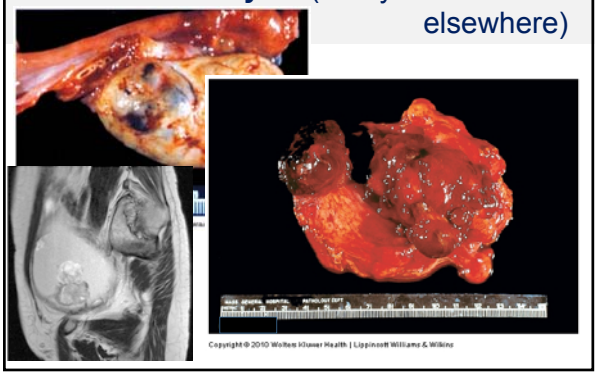
- Many have well-known precursor stages (endometriosis) which is prevalent in women
- Patients are relatively younger
- Not as well studied as in HGSC
- OCCC is resistant to carbo/taxol
- Actionable genes and pathways (?)



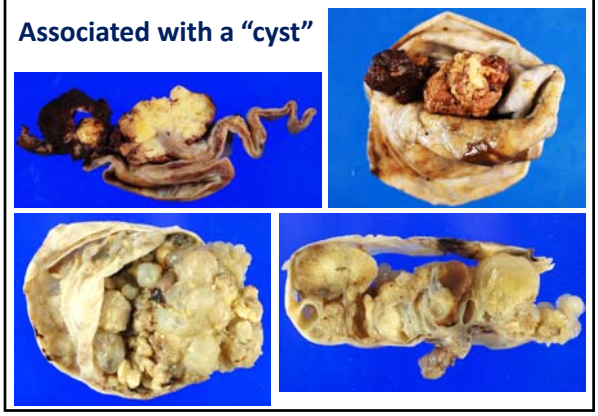
Endometriosis- intriguing & but problematic!



Arising from ovarian endometriosis- "endometriotic cyst" (rarely endometriosis elsewhere)

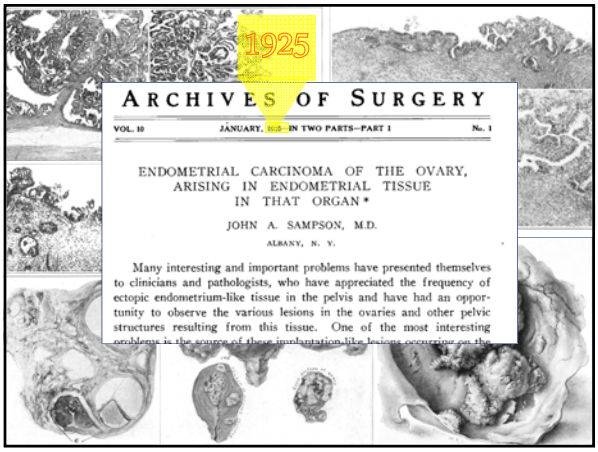


Associated with a "cyst"

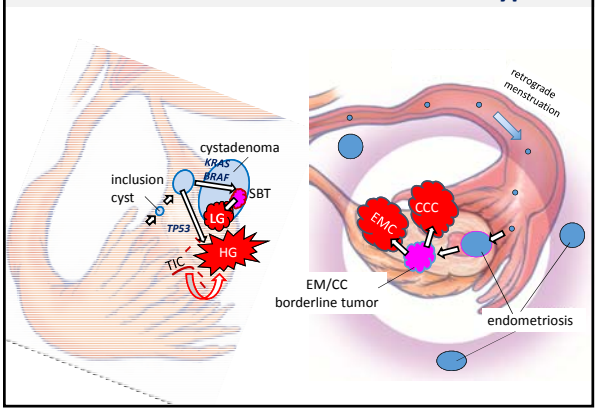


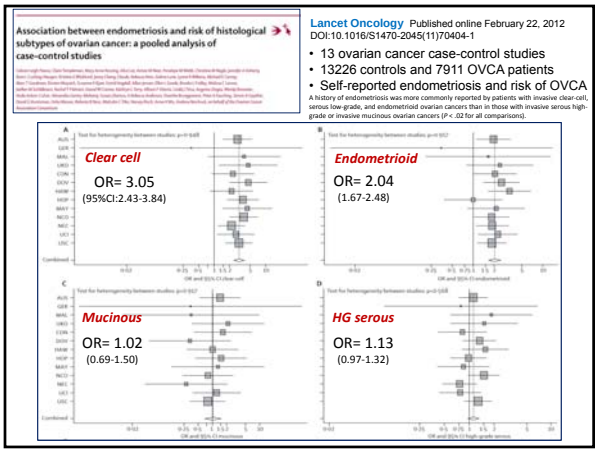
Endometriosis-related ovarian neoplasm

- Clear cell carcinoma
- Endometrioid carcinoma
- Seromucinous tumor

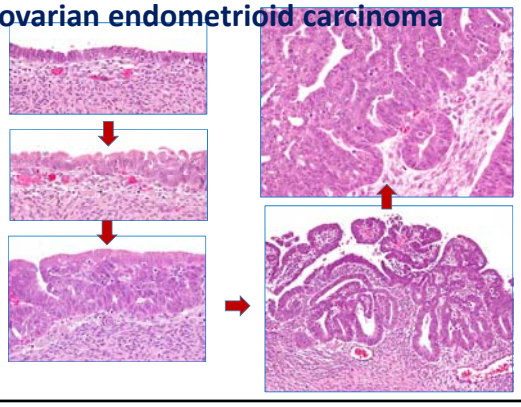


Genesis of different ovarian cancer subtypes

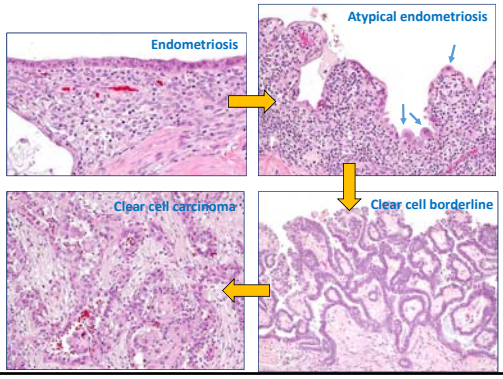




Progression from endometriosis to ovarian endometrioid carcinoma



Progression from endometriosis to ovarian clear cell carcinoma



Serous carcinoma is closer to normal fallopian tube epithelium in gene expression profile analysis

Carcinoma	Normal ovary	Fallopian tube	Colon	Endometrium
Clear cell	0.9623	0.7791	0.6775	**0.0002**
Endometrioid	0.4915	0.5928	0.9748	**0.0172**
Serous	0.0743	**0.0042**	0.9993	0.8504
Mucinous	0.6905	0.4863	**0.0003**	0.9860

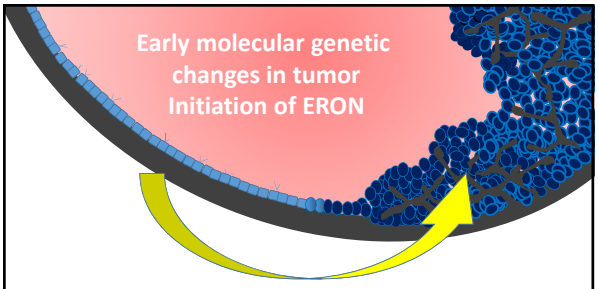
rank-sum analysis

Human Cancer Biology Clin Cancer Res 2005, 11:6116

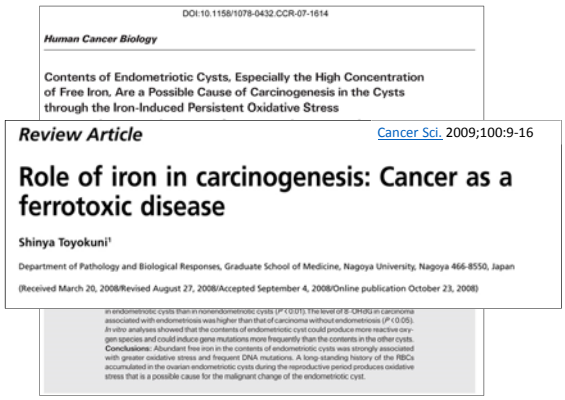
Patterns of Gene Expression in Different Histotypes of Epithelial Ovarian Cancer Correlate with Those in Normal Fallopian Tube, Endometrium, and Colon

Rebecca T. Marquez,[2] Keith A. Baggerly,[2] Andrea P. Patterson,[1] Jinsong Liu,[5] Russell Broaddus,[5] Michael Frumovitz,[2] Edward N. Atkinson,[2] David I. Smith,[6] Lynn Hartmann,[6] David Fishman,[7] Andrew Berchuck,[8] Regina Whitaker,[8] David M. Gershenson,[1] Gordon B. Mills,[4] Robert C. Bast, Jr.,[1] and Karen H. Lu[3]

Clonal relationship between ERON and associated endometrioma



PTEN LOH & mutation	Sato, Cancer Res, 2000
PIK3CA mutation	Yamamoto, J Pathol, 2011 Matsumoto, AJCP, 2015
ARID1A mutation	Ayhan, Int J Gyn Can, 2012 Yamamoto, Mod Pathol, 2012
CATNNB1 mutation	Matsumoto, AJCP, 2015



DOI:10.1158/1078-0432.CCR-07-1614

Human Cancer Biology

Contents of Endometriotic Cysts, Especially the High Concentration of Free Iron, Are a Possible Cause of Carcinogenesis in the Cysts through the Iron-Induced Persistent Oxidative Stress

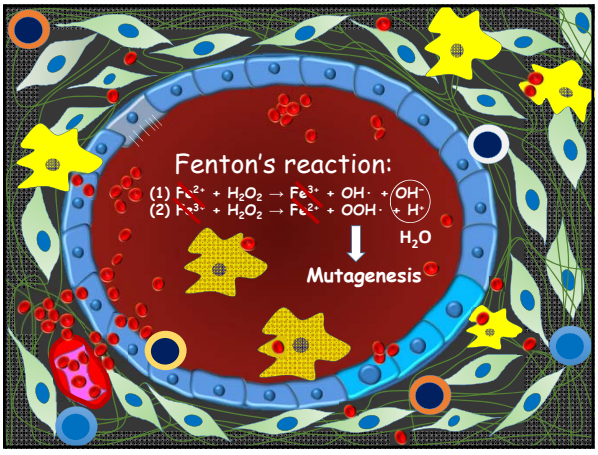
Review Article Cancer Sci. 2009;100:9-16

Role of iron in carcinogenesis: Cancer as a ferrotoxic disease

Shinya Toyokuni[1]

Department of Pathology and Biological Responses, Graduate School of Medicine, Nagoya University, Nagoya 466-8550, Japan

(Received March 20, 2008/Revised August 27, 2008/Accepted September 4, 2008/Online publication October 23, 2008)



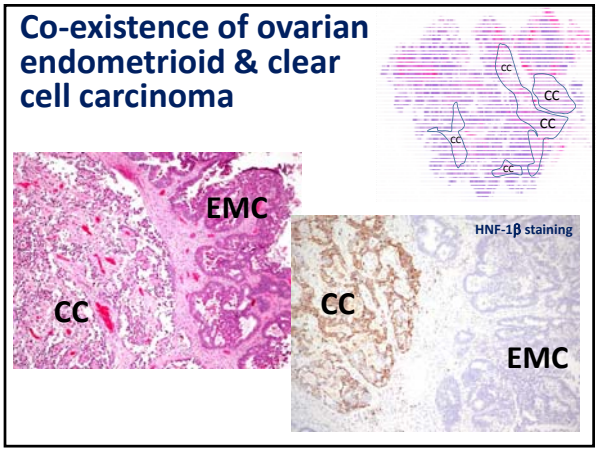
Ovarian Clear Cell Carcinoma

- Half of cases are stage I
- Adv. stage tumors are refractory to platinum-based therapy
- Always ER negative
- Role of irradiation therapy
- Expression of HNF1-β & Napsin A & α-methylacyl-coenzyme A racemase (AMACR, P504S)

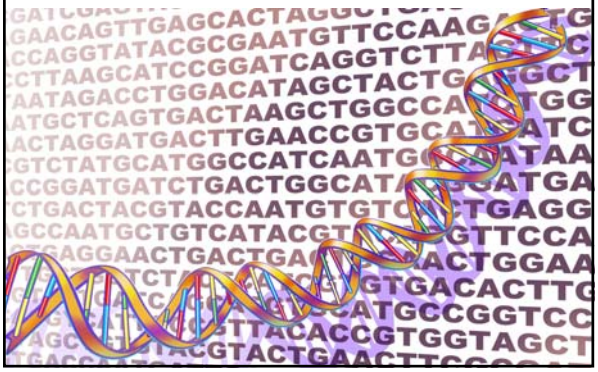
Endometrioid Carcinoma

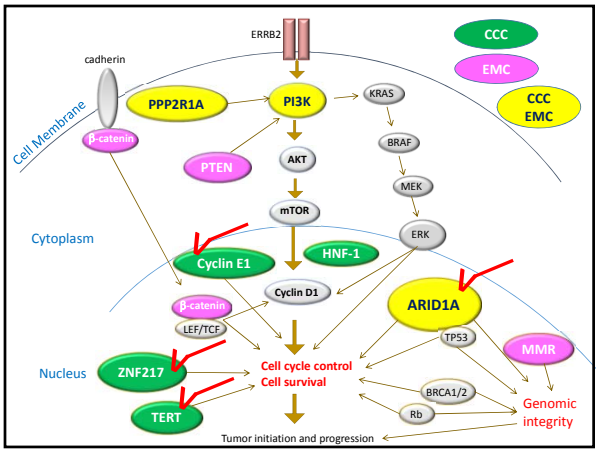
- Most are stage I
- Always ER positive and low-grade
- Morphologically & molecularly similar to uterine endometrioid CA
- Not unusually to have synchronous uterine endometrioid CA

Co-existence of ovarian endometrioid & clear cell carcinoma



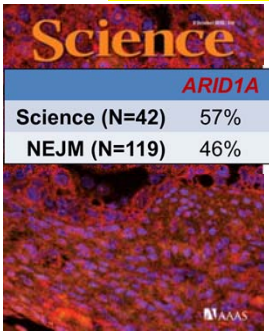
Molecular Alterations in ERON





Somatic mutation of ARID1A

AT-rich interactive domain 1A (ARID1A)



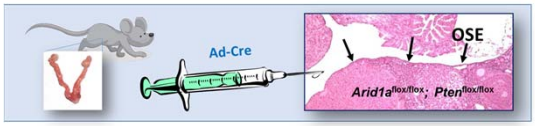
Science

Frequent Mutations of Chromatin Remodeling Gene *ARID1A* in Ovarian Clear Cell Carcinoma

	ARID1A	PIK3CA	PPP2R1A	KRAS
Science (N=42)	57%	40%	7.1%	4.7%
NEJM (N=119)	46%	-	-	-

Associated Ovarian Carcinomas

Mouse Models of ARID1A Deletion



ARID1A del ➡ **nothing happening**

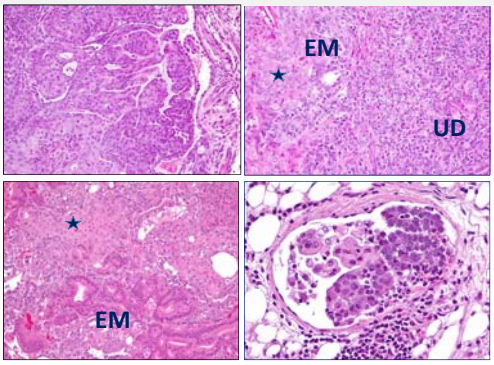
ARID1A del + Pten deletion ➡ **endometrioid/undiff-like CA**

ARID1A del + PIK3CA mut ➡ **clear cell-like CA**

ARID1A del + Apc/Pten defective ➡ **endometrioid-like CA with epithelial differentiation and prolongs survival**

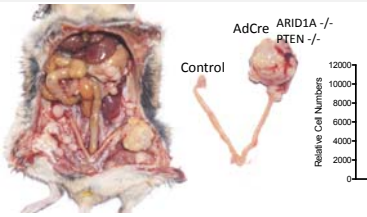
JNCI 2014; PMID: 24899687
Nat Comm 2015; PMID: 25625625
J Pathol, 2015; PMID: 26279473

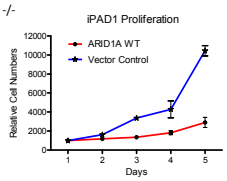
Induced PTEN/ARID1A Deletion (iPAD)

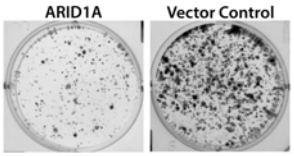


JNCI 2014; PMID: 24899687

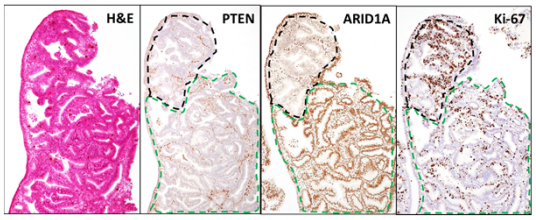
ARID1A loss is required for tumor growth

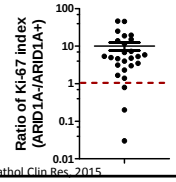


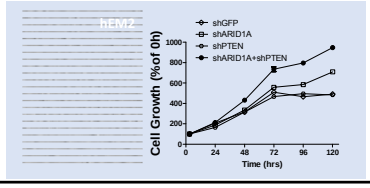




Co-loss of ARID1 and PTEN enhances proliferation in AH/EIN

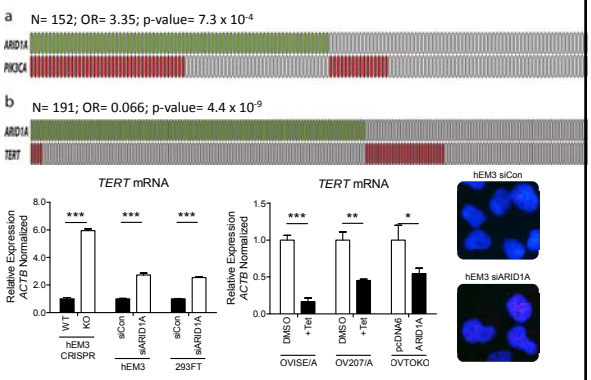




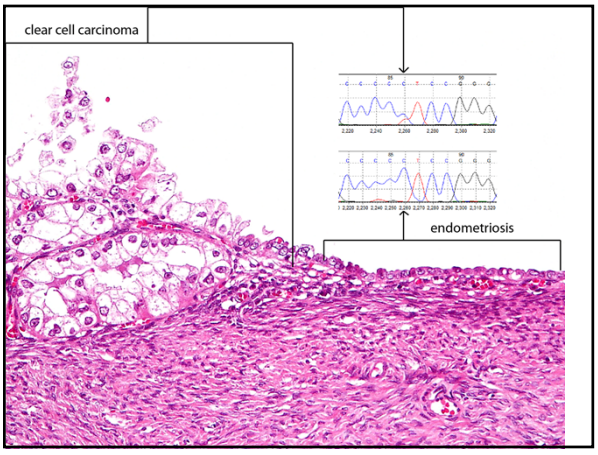


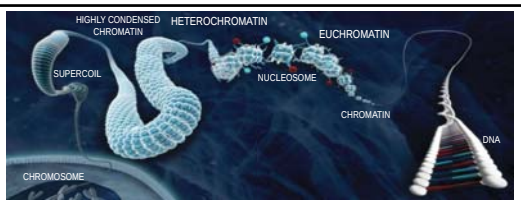
J Pathol Clin Res. 2015

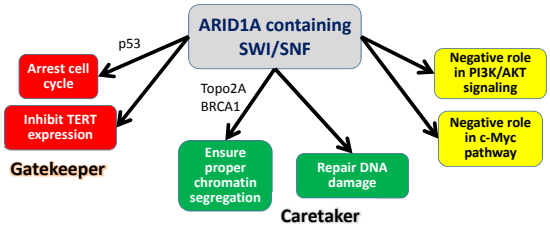
ARID1A negatively regulates hTERT promoter activity



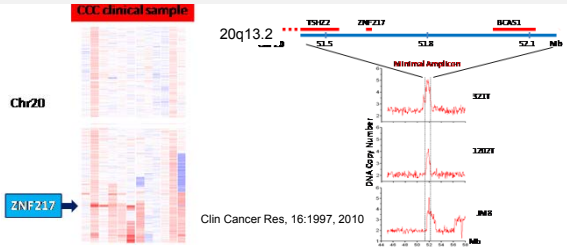
PNAS 2013 ; Mod Pathol. 2011; Am J Pathol. 2011; J Pathol. 2014; unpublished







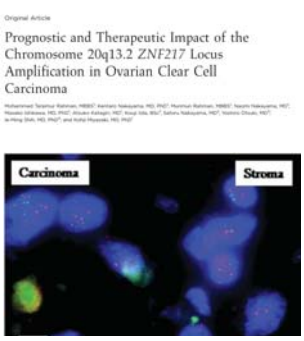
CCNE1, ZNF217 & *PPMID* are amplified in ovarian CCC

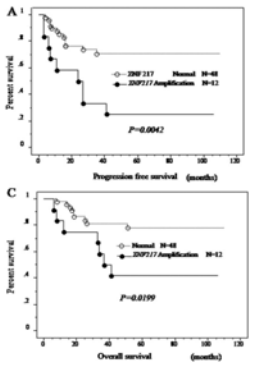


Clin Cancer Res. 2003 Jun;9(6):1995-2004.
Association of 17q21-q24 gain in ovarian clear cell adenocarcinomas with poor prognosis and identification of PPM1D and APPBP2 as likely amplification targets.

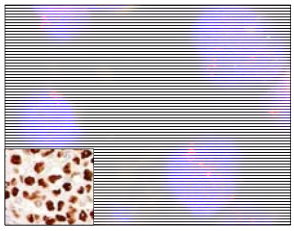
Clin Cancer Res. 2009 Apr 1;15(7):2269-80.
PPM1D is a potential therapeutic target in ovarian clear cell carcinomas.

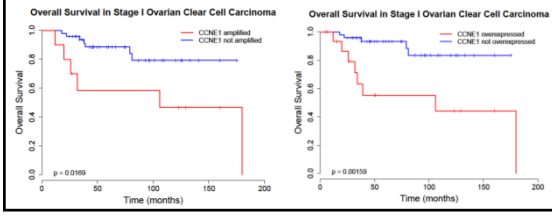
ZNF217 amplification and clinical outcome



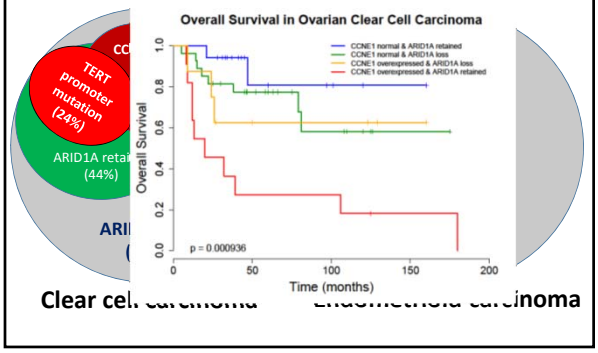


CCNE1 amplification and overexpression in ovarian CCC





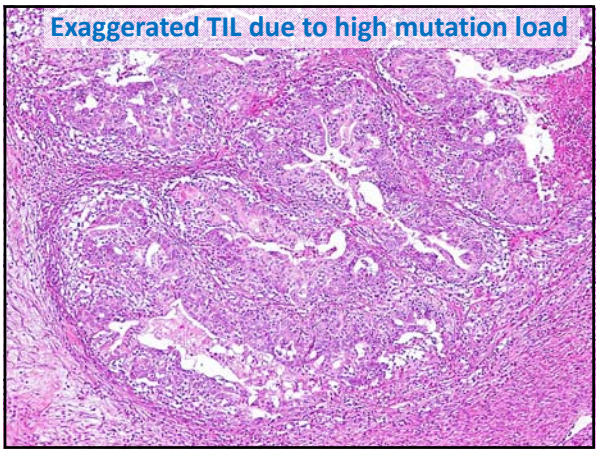
Cyclin E1^{high}, ARID1A^{retain} identifies a subset of OCCC with the worse outcome

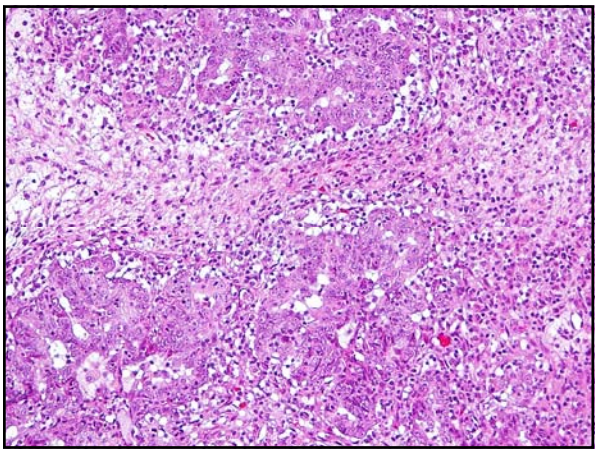


Seromucinous carcinoma

- Uncommon ovarian cancer
- Arise from seromucinous borderline tumor
- Mixed epithelial types
- Inflammatory microenvironment

Int J Gynecol Pathol. PMID:22653341

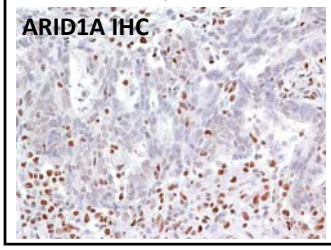




Exome sequencing in a seromucinous carcinoma of the ovary (49 y/o, stage IC)

783 genes somatic mutations (>50-fold more mutations) than the other tumors

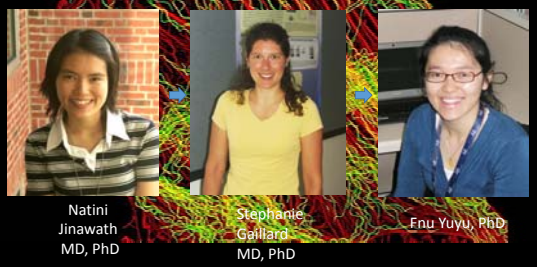
Somatic nonsense mutation in ***MSH2*** (g.chr2 : 474969666C > T; c.970C > T; p.324Q >X).



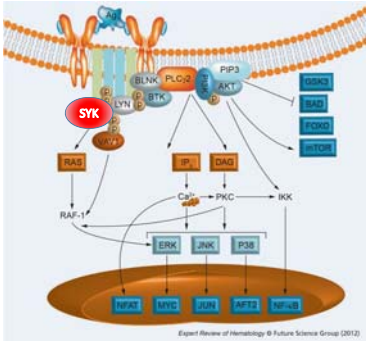
ARID1A
5543insG; 6415delC
PIK3CA
88R/Q

J Pathol, 2012, PMID:22102435

Targeting Spleen Tyrosine Kinase to Potentially Sensitize Anti-microtubule Agents in Ovarian Cancer

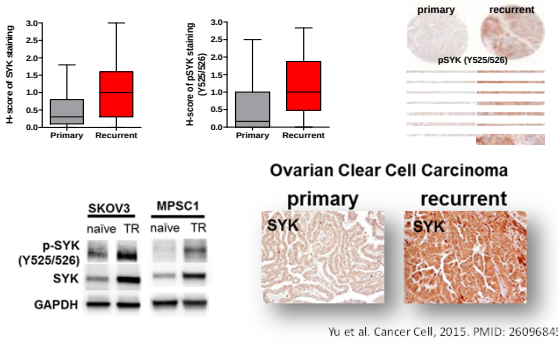


Spleen Tyrosine Kinase (SYK)



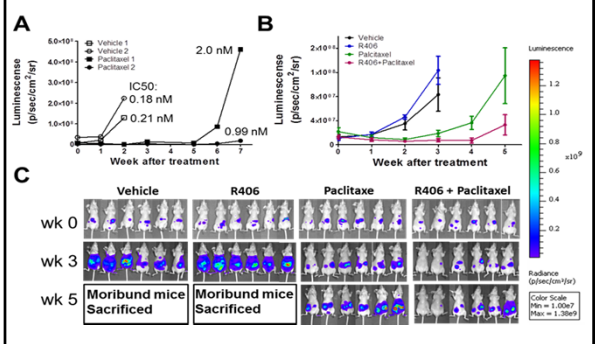
- A non-receptor tyrosine kinase mediates signal transduction of transmembrane receptors immunoreceptors & integrins.
- Activated SYK signaling is essential for proliferation and survival in B-cell malignancies.
- The biological role of SYK in solid tumors, however, remains largely elusive, but it appears to be cell type specific.

SYK expression in recurrent post-chemotherapy OVCA tissues and paclitaxel-resistant cells



Yu et al. Cancer Cell, 2015. PMID: 26096845

SYK inhibitor & paclitaxel combination significantly inhibit paclitaxel-resistant i.p. tumor xenografts



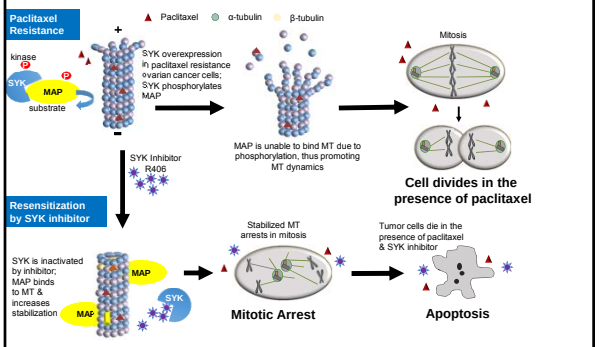
Yu et al. Cancer Cell, 2015. PMID: 26096845

Phosphoproteomic analysis *in vitro* reveals the effect of SYK inhibition on molecules in organization of cytoskeleton including microtubule dynamics

Gene symbol	Full Name	Phosphopeptide	Protein Phosphorylation site	Average H/L ratio
DCTN2	dynactin 2 (p50)	TGYESGEyEMLGEGLGVK	Y91	0.61
MAP1B	microtubule-associated protein 1B	AAEAGGAEEQyGFLTTPTK	Y1082	0.48
		SPPLIGSESAyESFLSADDKASGR	Y1410	0.68
		ESSPLySPTFSDSTSAVK	Y1796	0.49
		TSDVGGyYYEK	Y1904	0.57
		TSDVGGYYyEK	Y1906	0.57
		SPSDSGySYETIGK	Y1921	0.56
		SPSDSGYSyETIGK	Y1923	0.54
		TPEDGDySYEIEK	Y1938	0.44
		TPEDGDYSyEIEK	Y1940	0.54
		TPDTSTyCYETAEK	Y2040	0.53
		TPDTSTYCyETAEK	Y2042	0.53
MAP4	microtubule-associated protein 4	KVSySHIQSK	Y1001	0.54
TBCB	tubulin folding cofactor B	LGEyEDVSR	Y98	0.73
TUBA 4A, 3E, 3D, 3C, 1C, 1B, 1A	tubulin alpha 4a, 3e, 3d, 3c, 1c, 1b, 1a	IHFPLATyAPVISAEK	Y272	0.39
TUBA8, 4A, 3D, 3C, 1C, 1B, 1A	tubulin alpha 8, 4a, 3d, 3c, 1c, 1b, 1a	QLFHPEQLITGKEDAANNyAR	Y103	0.54
TUBA8, 4A, 3E, 3D, 3C, 1C, 1B, 1A	tubulin alpha 8, 4a, 3e, 3d, 3c, 1c, 1b, 1a	VGINyQPPTVVPGGDLAK	Y357	0.38
TUBB	tubulin, beta	ISVYyNEATGGK	Y51	0.51

Yu et al. Cancer Cell, 2015. PMID: 26096845

Combination of SYK inhibitor & paclitaxel



Yu et al. Cancer Cell, 2015. PMID: 26096845

Summary

- ERONs include thre… frequently associat… endometrioma.
  - **Endometrioid carcinoma**
  - **Clear cell carcinoma**
  - **Seromucinous carcinoma**
- Characterized by shared and unique molecular alterations. Several are actionable.
- Mutation in *ARID1A* tumor suppressor is common. Required PI3K/PTEN alterations.
- Understanding their pathogenesis helps outcome prediction and development of better therapy.

Questions to be addressed:

- Molecular landscape of endometriosis.
- Molecular decisions in developing CCC vs. EMC.
- Ovarian microenvironment and ERON pathogenesis.
- The translational roles of *ARID1A* mutations.
- Identifying endometriomas with increased risk.
- Clinical studies to demonstrate the efficacy of targeted therapy.
- Immune checkpoint inhibitors in ERONs with MMR deficiency.

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