Molecular Gynaecological Pathology

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Outline

• Cervix
  - HPV infection
  - p16 immunostaining
• Vulva
  - HPV-associated
  - Non-HPV-associated
• Endometrium
  - Type I and type II tumours
  - Hybrid tumours
• Ovary and Fallopian tube
  - Dichotomous pathways (type I and II tumours)
  - ‘p53 signatures’ and TIC
• Emerging areas
  - FOXL2
  - Aggressive angiomyxoma
  - Endometrial stromal tumours
HPV and Squamous Neoplasia

HPV Infection → De-regulation of E6/E7 (p16 positive)

Normal ↔ Low Grade IN ↔ High Grade IN

Telomerase Activation
Inhibition of Apoptosis
Genetic Changes
Immune Response
Smoking

Invasive Cancer
Human Papillomavirus Infection and Anogenital Disease

- HPV infection is present in 99.7% of invasive cervical carcinomas

- Mucosal HPV infection can also cause vulval and vaginal pre-cancerous lesions and genital warts
The Papillomavirus Life Cycle

Doorbar J Clin Sci 2006;110:525-41
HPV and Neoplastic Progression

Doorbar J *Clin Sci* 2006;110:525-41
What Governs Progression?

• HPV type
  - High-risk HPV types, particularly 16 and 18
• Persistence of HPV infection
• Up-regulation of E6/E7
• Loss of capacity to replicate viral DNA
• HPV integration
  - Chromosome sites random
  - Viral breakpoint consistent (E1/E2)
The Effects of High-Risk HPV E6/E7 Expression
p16\textsuperscript{\textsc{INK4A}} in Squamous Lesions
p16$^{\text{INK4A}}$ in Glandular Lesions
Two Pathways to Vulval Neoplasia

HPV-related

• Young women
• Warty/basaloid (undifferentiated) vulvar intraepithelial neoplasia (VIN)
• Warty/basaloid carcinoma
• Associated with other intraepithelial lesions
• Same HPV types as CIN
• Predominance of HPV 16
• Mechanisms probably similar
Two Pathways to Vulval Neoplasia

Non-HPV-related

- Older women
- Associated with lichen sclerosus
- Differentiated (simplex type) VIN
- Well differentiated squamous cell carcinoma but clinically aggressive
- p16 negative; ? p53 mutation important
Endometrial carcinoma

Type I tumours

- Endometrioid and mucinous phenotypes
- *PTEN, CTNNB1, KRAS, PIK3CA* mutations
- *PTEN* loss and mutation identifiable in morphologically normal proliferative glands
- Microsatellite instability
  - Germline mutation of MMR genes
  - Promoter hypermethylation esp *hMLH1*
Endometrial Carcinoma

• Type II tumours
  - Serous and clear cell phenotypes
  - *p53* mutation and overexpression
  - Inactivation of *p16* and *E-cadherin*
  - *PPP2R1A* mutation in 41% of serous
    • McConechy et al J Pathol 2011; 223: 567-573

• Mixed tumours
  - Overlapping morphological and molecular features
  - ? Dedifferentiation by acquisition of *p53* mutation
Endometrioid Ca

Normal epithelium

Non-endometrioid Ca

Chromosome Instability
- LOH
- E-cadherin
- MI, PTEN
- β-catenin
- PPP2R1A?

P53

High-grade endometrioid Ca

BAX
- TGFβ-RII
- IGF-IIR
- MSH3
- MSH6

Cyclin D1
Cyclin E
STK15

P53
# Ovarian Surface Epithelial Tumours

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*Gilks CB. Int J Gynecol Pathol 2004; 23: 200-205*
High-Grade Serous, Endometrioid and Unclassified Tumours

• Loss of BRCA1/BRCA2 function
  - Germline/somatic mutation; loss of heterozygosity
  - Promoter hypermethylation
  - Amplification of EMSY

• Unable to repair dsDNA breaks
  - Complex karyotypes

• \textit{p}53 mutation common in high-grade serous carcinoma (almost 100%)
  - Ahmed et al J Pathol 2010; 221: 49-56

• WT1 immunopositive
High Grade Serous Carcinoma

CK7, Ca125, EP4, WT1 +ve
CK20, CEA, Calretinin -ve
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Low-grade serous tumours

• *BRAF* and *KRAS* mutation common in borderline and invasive tumours (60-65%)
• *p53* mutation uncommon (<10%)
• Often diploid
• Fewer karyotypic and other molecular abnormalities than high-grade tumours

• Diagnosis?
  - Two-tier grading system based on nuclear atypia alone

• Treatment?
  - Differences in chemosensitivity
    • Santillan A et al Int J Gynecol Cancer 2007; 17: 601-606
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Low-Grade Endometrioid Tumours

- Association with endometriosis and endometrioid hyperplasia
- Endometriotic cysts
  - often monoclonal
  - LOH reported
- **Beta-catenin** mutation common (16 - 54%)
  - occurs in endometriosis and tumours
- **PTEN** mutation frequent (20%)
- **ARID1A** mutation in 30%
  - associated with BAF250a loss (Wiegand et al NEJM 2010; 363: 1532-1543)
- Boundary with high-grade tumours?
  - Use beta-catenin/PTEN vs BRCA1/BRCA2?
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Clear Cell Carcinoma

- Associated with endometriosis
- Occur in BRCA1 / BRCA2 mutation carriers
- ARID1A mutation in 46% of endometriosis-associated tumours (Wiegand et al NEJM 2010; 363: 1532-1543)
- Not clear if can separate low and high grade groups
- Some evidence that tumours associated with endometriosis less aggressive than those associated with clear cell adenofibroma
- Recent improvement in definition (WT1 neg, p53 neg, ER neg, HNF1β pos) will help further study
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Mucinous Tumours

• Borderline tumours and invasive carcinomas
  - Endocervical (Mullerian) type
  - Intestinal type
• Primary tumours are uncommon (6 of 220 ovarian carcinomas)
  - Seidman et al. Int J Gynecol Pathol 2004; 23: 41-4
• Individual tumours are heterogeneous
  - Benign, borderline and invasive components
• \textit{KRAS} but not \textit{BRAF} mutations common
• Must rigorously exclude metastases, including pseudomyxoma peritonei
Well Differentiated Mucinous Adenocarcinoma
Benign-Borderline Transition
Dichotomous Pathways

• Type I tumours
  - Serous, mucinous: cystadenomas and borderline tumours
  - Endometrioid, clear cell: endometriosis

• Type II tumours
  - High-grade serous, endometrioid, transitional, undifferentiated

Kurman and Shih. Int J Gynecol Pathol 2008; 27: 151-60
BRCA / p53  

BRAF / KRAS  

Russell SHE & McCluggage WG. J Pathol 2004; 203: 617-619
Fallopian tube serous carcinogenesis


Salvador et al. The fallopian tube: primary site of most pelvic high-grade serous carcinomas. *Int J Gynecol Cancer* 2009; 19: 58-64
Pelvic Serous Carcinogenesis

Xian et al, J Pathol 2010; 220: 17-23
Emerging Areas

• *FOXL2* mutation in adult-type granulosa cell tumours

• *HMGA2* expression in aggressive angiomyxoma

• Defining translocations in endometrial stromal tumours
FOXL2 in ovarian sex cord-stromal tumours

- C134W FOXL2 mutation identified in 4 index adult-type granulosa cell tumours
- Present in 86/89 (97%) aGCTs, 3/14 thecomas, 1/10 jGCTs
- Absent in 49 other sex cord stromal tumours and 329 other ovarian and breast tumours

- Shah et al NEJM 2009; 360: 2719-2729
FOXL2 in ovarian sex cord-stromal tumours

- C134W mutation in 53/56 aGCTs, 2/6 thecomas but none of remaining 1281 tumours from a range of sites
  - Kim et al J Pathol 2010; 221: 147-152
- Mutation present in 18/20 aGCT and 0/3 jGCTs
  - Kim et al Histopathology 2010; 56: 408-410
- Mutation present in 52/56 aGCTs; 3/4 negative cases mis-diagnosed
  - Jamieson et al Mod Pathol 2010; 23: 1477-1485
- FOXL2 immunohistochemistry sensitive (80%) and specific (99%) marker of SCSTs but not aGCT specifically
Translocations in endometrial stromal tumours

- Recurrent translocations present in endometrial stromal nodules and sarcomas
- $t(7;17)(p15;q21)$ leads to fusion of $JAZF1$ and $JJAZ1$
- Present in 92% of ESNs and 70% of low-grade ESSs
  - Chiang & Oliva Adv Anat Pathol 2011; 42: 609-617
Translocations in endometrial stromal tumours

• Variant translocations and fusions increasingly described
  - JAZF1/PHF1; EPC1/PHF1
  - YWHAE gene rearrangement ? higher grade histology
    • Lee et al Mod Pathol 2011; 24: 255A

• Undifferentiated uterine sarcoma
  - Uniform type - JAZF1/JJAZ1 in 1/3
  - Polymorphic type - JAZF1/JJAZ1 in 0/3
  - Low-grade - present in 6/12
Summary

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