Genomic analysis of low-grade serous ovarian cancer reveals unique therapeutic vulnerabilities

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Peter MacCallum Cancer Centre
Cancer Genetics Lab (Professor Ian Campbell)
Serous ovarian cancer segregates into low- (LGSOC) and high grade (HGSOC)

Low-grade serous ovarian cancer
- ~5% of EOCs diagnosed
- RAS/RAF pathway frequently mutated
- Low-level DNA copy number change
- TP53 wild-type
- Younger age of onset (45-57 years)
- Chemo resistant (increased recurrence)

High-grade serous ovarian cancer
- ~75% of EOCs diagnosed
- RAS/RAF pathway wildtype
- Widespread DNA copy number change
- TP53 mutated
- Older age of onset (55-55 years)
- Usually platinum sensitive
Survival analysis of LGSC compared to HGSC

**Entire cohort**
- Our LGSOC cohort (n=77)
- TGCA HGSOC cohort (n=630)
- COEUR HGSOC cohort (n=1245)

**Residual disease**
- Our LGSOC cohort (n=20)
- TCGA HGSOC cohort (n=503)
- COEUR HGSOC cohort (n=458)

Cécile Lepage (Canadian Ovarian Experimental Unified Resource)
Current MEKi trials for LGSOC

- Response in a subset of patients likely suggests that in the \textit{RAS/RAF} mutation carriers there are other pathway alterations which can bypass the dependency of \textit{RAS/RAF}
- Identify and functionally validate novel drivers in \textit{RAS/RAF} negative cases

\begin{itemize}
  \item \textbf{KRAS G12V (Selumetinib)}
  \item \textbf{BRAF V600E (Dabrafenib)}
  \item \textbf{NRAS Q61K (Trametinib)}
\end{itemize}

Farley \textit{et al.} (2013)

Moujaber \textit{et al.} (2018)

Champer \textit{et al.} (2019)
Generation of the candidate LGSOC targeted gene panel

Whole-exome studies

Etemadmoghadam et al (2017)
21 LGSOCs

9 LGSOCs, 13 serous borderline tumours (SBTs)

Jones et al (2012)
9 LGSOCs

Sequenced 127 candidate genes (full-exon coverage) in 71 FFPE derived LGSOCs

39 LGSOCs
13 SBTs
Somatic mutation profile of the low-grade serous ovarian cancer cohort
Copy number analysis of low-grade serous ovarian carcinomas

| Chromosome | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | X |
|------------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| KRAS/BRAF/NRAS +ve (n = 26) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| USP9X +ve, KRAS/BRAF/NRAS +ve (n = 7) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| USP9X +ve, KRAS/BRAF/NRAS -ve (n = 12) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KRAS/BRAF/NRAS/USP9X -ve, somatic driver +ve (n = 18) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KRAS/BRAF/NRAS/USP9X /somatic driver -ve (n = 9) | | | | | | | | | | | | | | | | | | | | | | | | | | |
USP9X appears to act as a haploinsufficient tumor suppressor gene

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<th>USP9X protein change</th>
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- USP9X appears to escapes promoter methylation
- USP9X haploinsufficiency has been documented

• + 8 samples with USP9X copy loss
Functional validation of USP9X knockdown

Proteins down-regulated in VOA4627 cells following knockdown

VOA4627

VOA6406

Abhimanyu Nigam

Deubiquitylating enzyme USP9x regulates hippo pathway activity by controlling angiomotin protein turnover

Hui Thanh Nguyen, Dina Andreeva, Raju Gupta, Chasantham Choudhary, Xi Houng, Ritter JA Sibthorpe, Anand C Loye & Stephen R Cole

Cell Discovery 2, Article number: 26001 (2016) | Download Citation

renal clear cell carcinomas
Future directions for the study

- ~40 additional LGSOC samples to sequence
- phosphor MAPKp44/p48, ERK1/2 IHC on TMA – Dr Martin Koebel
- Identify the molecular context of USP9X-regulated processes across our LGSOC cell line panel
# Faculty Disclosure

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<th>Honoraria/ Expenses</th>
<th>Consulting/ Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/ Patent</th>
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Acknowledgments

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- Tim Semple

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- Prof Anna deFazio
- Leanne Bowes
- Joy Hendley

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- Samantha Cosh (Mater Research Institute)