Integrated Molecular Characterization of Uterine Carcinosarcoma (UCS)

TCGA Research Network
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Background

- UCS contains an admixture of carcinoma (epithelial component) and sarcoma (mesenchymal component)
- Rare, aggressive tumor, found in <5% of all uterine cancers
- 5 year survival rate is about 35%
- Median survival of 24 months, compared to 60 months for endometrial cancer (UCEC)
- Median age of patients is 65 years, mostly occurring in post-menopausal women
- Symptoms include vaginal bleeding, abdominal pain, and polyps
- TCGA collected 57 samples for the UCS project
Carcinosarcoma histologic classification

- Sarcomatous components are classified as homologous or heterologous based on whether they reflect tissue types normally found within the uterus.
  - Homologous (found in the uterus), commonly, undifferentiated stromal sarcoma; associated with more favorable prognosis than heterologous
  - Heterologous (found external to the uterus), commonly, rhabdomyosarcoma

Ack: Rob Soslow
Heterogeneous disease – no robust clusters found

Copy number aberrations unsupervised clustering

Ack: Chip Stewart, Andrew Cherniack
Landscape of DNA aberrations in UCS

Ack: Chip Stewart, Andrew Cherniack
Potential therapeutic opportunities in UCS

Ack: Brad Murray
UCS vs. endometrial (UCEC) and ovarian (OV) cancers

Ack: Hui Shen
Pan-Cancer EMT scores – UCS has the largest range of values

Ack: Lauren Byers, Vonn Walter
Epithelial to mesenchymal transition (EMT) in UCS

Promoters for miR-200 family

Ack: Vonn Walter et al.
Pan-cancer proteomics comparison of UCS

DNA damage response

EMT

Cell signaling
Competing theories of development of UCS

1. **Collision theory**: A collision between adjacent, independent carcinomas and sarcomas

2. **Combination theory**: A combination of cellular masses that diverged early from a common precursor stem cell

3. **Conversion theory**: Monoclonal origin with late divergence of the carcinoma into the sarcoma
73% of all mutations, 82% in SMGs are clonal in UCS

Similar to most other tumor types

Supports the conversion theory

Ack: Chip Stewart, Andrew Cherniack
Summary

- UCS is a rare, aggressive tumor, found in <5% of uterine cancers
- Median survival of 24 months, compared to 60 months for endometrial cancer (UCEC)
- Very heterogeneous disease with poor clusters
- Extensive CNVs and recurrent mutations in TP53 (91%), FBXW7 (39%), PIK3CA (35%), PPP2R1A (28%), PTEN (19%)
- Identified DNA aberrations with potential therapeutic relevance
- Most UCS samples resemble serous endometrial and ovarian cancer samples, with TP53 mutations and high CNVs, but a few samples resemble endometrioids with PTEN mutations and low CNVs
- UCS spans a large range of EMT scores compared to other tumors
- Promoters of miR-200 family are methylated in samples with high EMT scores, with correspondingly low miR-200 expression
- UCS shares DNA damage response and cell signaling proteomic features with gynecological tumors, but EMT features with non-epithelial tumors
- Most of the mutations are clonal, supporting the conversion theory of UCS tumor development
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