Classification and Genetics of Sarcomas

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Sarcomas

- Heterogeneous tumors of mesenchymal origin
- Two main classes
  - Bone sarcomas
  - Soft-tissue sarcomas
- More than 100 different histopathological subtypes defined
- About 50% of cases are associated with characteristic somatic molecular abnormalities, often gene fusions
- Many are associated with germline predisposition syndromes
Bone Sarcomas

• < 0.2% of human cancers
• ~3,000 cases a year; ~1,500 deaths a year
• Most often occur in children, adolescents and young adults
• Most common subtypes
  • Osteosarcoma (35%)
  • Chondrosarcoma (30%)
  • Ewing sarcoma (16%)
    ○ Associated with EWS-FLI1 gene fusions
Soft-Tissue Sarcomas

• <1% of human cancers
• ~12,000 cases a year; ~4,500 deaths a year
• ~45% of over 100 subtypes are associated with a recurrent molecular or cytogenetic abnormality
• Different types can occur in different age groups
• Some subtypes with the associated abnormality:
  • Desmoplastic small round cell tumors (*EWSR1-WT1* fusions)
  • Mixoid liposarcoma (gene fusions involving *DDIT3*)
  • Infantile fibrosarcoma (gene fusions involving *NTRK*)
  • Alveolar rhabdomyosarcoma (gene fusions involving *PAX* and/or *FOXO*)
  • Clear cell sarcoma (gene fusions involving *EWSR*)
  • Epithelioid sarcoma (fusions involving *SMARCB1*)
Ewing Sarcoma

H&E, 200X: this image demonstrates a monotonous population of small blue round cells in a soft tissue tumor

Images provided by Deepika Sirohi, MD, University of Utah
Liposarcoma

H&E, 200X: this image demonstrates a well-differentiated liposarcoma with variable-sized adipocytes with nuclear atypia

Images provided by Deepika Sirohi, MD, University of Utah
Osteosarcoma

H&E, 200X: this image demonstrates a proliferation of atypical spindle cells with laying down of malignant osteoid

Images provided by Deepika Sirohi, MD, University of Utah
Undifferentiated Pleomorphic Sarcoma (UPS)

H&E, 200X: this image demonstrates an atypical fascicular proliferation of spindle cells with increased mitotic index

Images provided by Deepika Sirohi, MD, University of Utah
Three Classes of Sarcoma Genomes

• Simple karyotype with a defining translocation/gene fusion

• Simple or complex karyotype with a specific mutation

• Complex karyotype with multiple chromosomal rearrangements, duplications and deletions
Gene Fusions are Common Molecular Events in Sarcomas

Gene A

Gene B

Genomic rearrangement

Transcription

Gene A Gene B fusion transcript

loss of function / gain of function / novel function
Gene Fusion Detection Methods

• Fluorescence in-situ hybridization (FISH)
  • Break-apart FISH is commonly used to detect gene fusions in sarcomas

• PCR with primers specific to the two fusion partners

• DNA sequencing
  • Gene panel
  • Whole genome

• RNA sequencing
  • Gene panel
  • Whole transcriptome
Gene Fusion Detection Using Break-Apart FISH

Green and red fluorescently labeled probes flank the EWSR1 locus. Cells negative for an EWSR1 gene fusion have two yellow signals (overlap of the green and red). Cells with split red and green signals are positive for an EWSR1 gene fusion.

This image demonstrates a sarcoma positive for an EWSR1 rearrangement (red and green split signals).
Gene Fusion Detection Using Next-Generation Sequencing

Fusion Sequence

Concordant Reads

Split Reads

Spanning Reads
Clinical Utility of Molecular Testing for Sarcomas

- Arriving at diagnosis for cases with ambiguous histology
  - E.g. diagnosis of small round cell tumors
- Refining molecular subtype of disease
  - E.g. Alveolar subtype of rhabdomyosarcoma is associated with PAX-FOXO fusions
- Identifying treatment options
  - E.g. KIT and PDGFRA mutations in Gastro-Intestinal Stromal Tumors (GIST) are associated with response to Imatinib
- Confirmation of lesions with an unusual presentation (age, location, appearance)
  - E.g. Confirmation of a synovial sarcoma in a 76-year-old individual
- Aiding in diagnosis for cases with de-differentiated histology
Molecular Testing is Useful for Diagnosing Small Round Cell Tumors

- Homogeneous light microscopic appearance of small round-cell neoplasms

- Ewing sarcoma, rhabdomyosarcoma, mesenchymal chondrosarcoma, desmoplastic small round cell tumor, round cell liposarcoma, poorly differentiated synovial sarcoma, and neuroblastoma may present in this way

- Identification of a characteristic gene fusion can help make the diagnosis (e.g. EWS-FLI1 fusion in Ewing sarcoma)
Cancer Predisposition Syndromes with Increased Risk of Sarcomas

- Li-Fraumeni syndrome
  - Germline heterozygous inactivating mutations in TP53
  - Childhood-onset sarcomas
- Retinoblastoma syndrome
  - Germline heterozygous inactivating mutations in RB1
  - Osteosarcomas
- Familial adenomatous polyposis (FAP)
  - Germline heterozygous inactivating mutations in APC
  - Desmoid tumors
# Genetic Syndromes with Increased Risk of Sarcomas

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothmund-Thompson</td>
<td>\textit{RECQLA}</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Neurofibromatosis, Type 1</td>
<td>\textit{NF1}</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td>Costello</td>
<td>\textit{HRAS}</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Beckwith-Wiedemann</td>
<td>\textit{CDKN1C, H19, IGF2, KCNQ1OT1}</td>
<td>Rhabdomyosarcoma</td>
</tr>
</tbody>
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Take Home Messages

• Sarcomas are a heterogeneous group of diseases with over 100 subtypes defined by histopathology

• Genetic testing can help with the diagnosis, molecular subtyping, and treatment selection

• A significant fraction of sarcomas are associated with either a germline cancer predisposition syndrome or a genetic syndrome with other phenotypic features
References

1. www.sarcomahelp.org
2. www.sarcomaalliance.org
Disclosures/Potential Conflicts of Interest

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