The Role of Chromosomal Translocations in the Molecular Pathology of Sarcomas

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Overview of translocations in bone and soft tissue sarcomas

Importance of chromosomal translocations – consistency and specificity
Role in biology, diagnosis, and therapy

Translocations in alveolar rhabdomyosarcoma (RMS)
Common 2;13 translocation – generating PAX3-FKHR fusion
Single breakpoints – single fusion size
Variant 1;13 translocation – generating PAX7-FKHR fusion

Translocations in Ewing’s sarcoma
Common 11;22 translocation – generating EWS-FLI1 fusion
Breakpoint variability – generating variable sized fusions
Protein products – ETS transcription factor (FLI1) and RNA binding protein (EWS)
Variant translocations involving other ETS proteins with EWS or related FUS protein
Additional translocations in Ewing sarcoma-like tumors

EWS protein and related RNA binding proteins
Fusions involving EWS and transcription factor-encoding genes in other sarcomas
TET family of RNA binding proteins – multiple regions of homology
Additional fusions involving genes related to EWS in sarcomas
Exception – TCF12-CHN fusion in myxoid chondrosarcoma
Fusion protein function and specificity – relationship of fusion protein to target cell
Expanding story of EWS-ATF1 and related fusions – same fusion in different tumors
Clear cell sarcoma and angiomatoid fibrous histiocytoma
Other gene fusions associated with divergent tumor types

Methodologies for detection of chromosomal translocations
Considerations for use of established technologies (Southern, PCR, FISH)
Immunohistochemistry – strategy to detect fusion protein (example: DSRCT)
Available antibodies to detect fusion proteins - application to various tumors
Microarray analysis of fusion-positive sarcomas
Identification of downstream target genes and other cellular features
Example - Expression profiling of fusion positive and negative RMS
Use of microarray data to identify IHC markers for fusion-positive ARMS

Clinical utility of detection of chromosomal translocations
Differential diagnosis
Prognosis
Prognostic significance of sarcoma-associated gene fusions
Prognostic value of microarray data - example of fusion-positive ARMS
Minimal disease detection – example: Ewing’s sarcoma
Minimal disseminated disease in bone marrow
Minimal disease in peripheral blood stem cell collections

**Major Points:**

- These fusion genes are useful reagents in the differential diagnosis of bone and soft tissue sarcomas.

- The detection of these fusion products is complex because of multiple breakpoints and variant partners, and thus a negative result must be interpreted cautiously.

- The fusion of EWS or related genes to one of multiple transcription factor-encoding genes in many of these sarcomas complicates the use of EWS reagents in the differential diagnosis of these sarcomas. These fusions also raise an essential issue of the relationship of these aberrant fusion proteins to the specific tumor phenotype and target cell.

- Several examples have been found in which a fusion gene is associated with two or more completely unrelated tumor types, and thus these gene fusions are not absolutely specific for a single lineage.

- For several translocation-associated sarcomas, antibodies to the C-terminal fusion partner have been shown to be useful markers of the presence of the fusion protein.

- Microarray-based strategies to elucidate genes associated with these fusion-positive tumors and downstream targets of these fusion proteins are generating useful markers for differential diagnosis and prognosis of these tumors.

- A small number of studies have been performed to address the clinical significance of these fusion genes as minimal disease markers. In studies of Ewing’s sarcoma, potential utility has been found in the predictive value of minimal disseminated disease in bone marrow but not in the predictive value of minimal disease in peripheral blood stem cell collections.

**References:**

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