Solid Tumour Section
Mini Review

Soft tissue tumors: t(2;13)(q35;q14) in alveolar rhabdomyosarcoma

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Clinics and pathology

Phenotype / cell stem origin
Alveolar rhabdomyosarcoma (ARMS).

Epidemiology
Occurs in ~60% of ARMS cases; patients tend to be older children (and young adults) compared to those with t(1;13)-positive ARMS tumors.

Clinics
Tumors tend to show higher invasiveness compared to those with t(1;13)-positive ARMS tumors. In metastatic cases, there is a high incidence of bone marrow involvement.

Prognosis
Outcome is worse than in rhabdomyosarcoma cases without a translocation (including embryonal rhabdomyosarcoma and translocation-negative ARMS). In one study, patients with localized t(2;13) and t(1;13)-positive ARMS had comparable outcomes whereas a recent study with small numbers suggested that localized t(1;13) tumors had a better outcome than those with localized t(2;13) tumors. Among patients presenting with metastatic disease, those with t(2;13)-positive tumors had a significantly poorer outcome than those with t(1;13)-positive tumors. Note: these studies are based on molecular detection of the translocations.

Cytogenetics

Cytogenetics Morphological
Reciprocal balanced translocations are generally present in cases with the associated molecular fusion.

Cytogenetics Molecular
The product of the 2;13 translocation is amplified in ~10% of t(2;13)-positive cases.
**Additional anomalies**
Amplification events involving 2p24 and 12q14 (as determined by DNA-based array studies).

**Genes involved and proteins**

**PAX3**
- **Location**: 2q35
- **Protein**: Transcription factor - paired box (PAX) family.

**FOXO1 (FKHR)**
- **Location**: 13q14
- **Protein**: Transcription factor - forkhead box (FOX) family.

**Result of the chromosomal anomaly**

**Hybrid Gene**

**Note**
A variant PAX3-FOXO4 fusion (also known an PAX3-AFX1) associated with a (X;13)(q13;q35) has been identified in one ARMS case.

**Description**
The 2;13 translocation breaks within intron 7 of the PAX3 gene and intron 1 of the FOXO1 gene on chromosome 13 to generate PAX3-FOXO1 fusion gene as well as a reciprocal FOXO1-PAX3 fusion gene. In ~10% of PAX3-FOXO1-positive ARMS tumors, the FOXO1-PAX3 gene is not detectable.

**Transcript**
The PAX3-FOXO1 fusion transcript consists of the first 7 exons of PAX3 fused to FOXO1 exons 2 and 3, and the FOXO1-PAX3 fusion transcript consists of the first exon of FOXO1 fused to the last two exons of PAX3. In ~35% of PAX3-FOXO1-positive ARMS tumors (with evidence of PAX3-FOXO1 transcript), the FOXO1-PAX3 transcript is not detectable. There is evidence that the PAX3-FOXO1 fusion transcript is upregulated relative to the wild-type PAX3 transcript by a transcriptional mechanism.

**Fusion Protein**

**Description**
The PAX3-FOXO1 fusion gene has a 2508 nt open reading frame encoding an 836 amino acid fusion protein. This fusion protein is a transcription factor with a PAX3 DNA binding domain and FOXO1 transactivation domain.

**Expression / Localisation**
Nuclear.

Generation of chimeric genes by the 2;13 translocation in ARMS. The exons of the wild-type and fusion genes are shown as boxes above each map and the translocation breakpoint distributions are shown as line segments below the map of the wild-type genes.
Oncogenesis

Transcription dysregulation. At the cellular level there is evidence of alterations in control of growth, survival, differentiation, and motility. In conjunction with other genetic changes, recipient cells show transformation in culture and tumorogenesis in injected mice. A conditional knock-in mouse model of the PAX3-FKHR fusion has been generated and successfully produces ARMS tumors.

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