Molecular Pathogenesis and Diagnostic, Prognostic and Predictive Molecular Markers in Sarcoma

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KEYWORDS

• Molecular diagnostics • Molecular markers • Soft tissue tumor • Bone • Sarcoma • GIST

Key points

- Sarcomas are characterized by notable morphologic and molecular heterogeneity. Molecular studies in the clinical setting provide refinements to morphologic classification, and contribute diagnostic and predictive information.
- Sarcomas with simple genome can be driven by transcriptional deregulation, abnormal kinase signaling, or epigenetic reprogramming. This group of sarcomas can be identified with specific molecular markers.
- Sarcomas with complex genome show multiple, nonrecurrent molecular alterations. There are no specific molecular diagnostic markers for these tumors. Some prognostic information may be derived from loss of tumor suppressor genes. The high mutational load may make these tumors good candidates for immunotherapies relying on neoantigens.

ABSTRACT

Sarcomas are infrequent mesenchymal neoplasms characterized by notable morphological and molecular heterogeneity. Molecular studies in sarcoma provide refinements to morphologic classification, and contribute diagnostic information (frequently), prognostic stratification (rarely) and predict therapeutic response (occasionally). Herein, we summarize the major molecular mechanisms underlying sarcoma pathogenesis and present clinically useful diagnostic, prognostic and predictive molecular markers for sarcoma. Five major molecular alterations are discussed, illustrated with representative sarcoma types, including 1. the presence of chimeric transcription factors, in vascular tumors; 2. abnormal kinase signaling, in gastrointestinal stromal tumor; 3. epigenetic deregulation, in chondrosarcoma, chondroblastoma, and other tumors; 4. deregulated cell survival and proliferation, due to focal copy number alterations, in dedifferentiated liposarcoma; 5. extreme genomic instability, in conventional osteosarcoma as a representative example of sarcomas with highly complex karyotype.

OVERVIEW

Sarcomas are infrequent malignant mesenchymal neoplasms characterized by notable morphologic and molecular heterogeneity. The current World Health Organization classification recognizes more than 100 soft tissue and bone tumor types,

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more than 70 of which are sarcomas,[1] illustrating a nosologic complexity that reflects biologic complexity and leads to substantial challenges in diagnosis and clinical management. Sarcoma diagnosis is based on morphology, immunohistochemistry, and clinicopathological correlation. In addition, molecular studies in the clinical setting provide refinements to morphologic sarcoma classification, and contribute diagnostic information (frequently), prognostic stratification (rarely), and predictive information concerning specific therapies (only occasionally, but most excitingly). Much of the current molecular understanding of sarcomas derives from conventional karyotypic analysis, which has been extremely fruitful in this field over the past 25 years.[2] At the cytogenetic level, a binary distinction between sarcomas with simple karyotype versus those with complex karyotype has been long recognized, and provides a simple conceptual framework of some academic value but limited clinicopathological significance.[3] The molecular correlates of these cytogenetic presentations are recurrent genomic rearrangements and activating gene mutations for sarcomas with relatively simple karyotype, and multiple, diverse genomic events including gene amplifications and nonrecurrent rearrangements, for those with complex karyotype. Biologically, oncogenic mechanisms are better understood for sarcomas with simple karyotype, and fall typically into 2 broad categories: transcriptional deregulation or deregulated signaling. This is in contrast to sarcomas with highly complex karyotypes, which typically do not harbor single "driver" genetic alterations, and rather display nonspecific molecular changes that promote oncogenic traits, such as cell cycle deregulation or genomic instability.

In this review, we summarize the major molecular mechanisms that underlie sarcoma pathogenesis, highlighting those alterations that provide diagnostic, prognostic, or predictive information (the so-called "clinically actionable" alterations). The discussion focuses on representative mesenchymal tumor types, following a pathogenic classification combining cytogenetic/genomic information and molecular biologic features, as summarized in **Box 1**. We address 5 major molecular alterations, including the presence of chimeric transcription factors, in vascular tumors; deregulated kinase signaling, in gastrointestinal stromal tumor (GIST); epigenetic deregulation by oncometabolites, as a result of metabolic enzyme mutations in chondrosarcoma and other tumor types; deregulated cell survival and proliferation, due to extreme copy number alterations, in dedifferentiated liposarcoma (DDLPS); and extreme genomic instability in conventional osteosarcoma, as a representative example of sarcomas with highly complex karyotype. **Table 1** provides a noncomprehensive list of clinically actionable genetic alterations commonly encountered in soft tissue and bone tumors.

SARCOMAS WITH SIMPLE GENOME

Sarcomas with simple genomic profiles usually harbor a recurrent molecular aberration, either a balanced chromosomal rearrangement or a mutation in a known oncogene or tumor suppressor gene, which is critical for tumorigenesis and is considered the main oncogenic driver. These alterations are usually present in the context of a relatively stable genome, with a low mutational load and a (near) diploid karyotype; additional point mutations or copy number alterations may occur during tumor progression, frequently following reproducible patterns, in contrast with the remarkable variability observed in genomically complex sarcomas (**Fig. 1**).

TUMORS WITH CHIMERIC TRANSCRIPTION FACTORS: VASCULAR TUMORS

An expanding list of mesenchymal tumors contain recurrent balanced chromosomal rearrangements,

Box 1
Molecular genetic categories of soft tissue and bone tumors, and representative tumor types

1. Sarcomas with simple genome
   a. Tumors with chimeric transcription factors and transcriptional deregulation; eg, vascular tumors
   b. Tumors with deregulated kinase signaling; eg, gastrointestinal stromal tumor
   c. Tumors driven by oncometabolites (via epigenetic deregulation); eg, chondrosarcoma
   d. Tumors driven by primary epigenetic deregulation; eg, chondroblastoma
2. Sarcomas with complex genome
   a. Tumors with characteristic copy number alterations; eg, dedifferentiated liposarcoma
   b. Tumors with highly complex karyotypes; eg, osteosarcoma