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Soft tissue sarcoma: from molecular diagnosis to selection of treatment. Pathological diagnosis of soft tissue sarcoma amid molecular biology and targeted therapies

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During the past few years, differential diagnosis of soft tissue tumours has improved due to novel molecular diagnostic tools. Besides a better differentiation between different tumour entities the recognition of specific molecular aberrations may also help to identify novel therapeutic targets. One of the most promising examples of effective molecularly driven treatment is the gastrointestinal stromal tumour. Shortly after the detection of gain-of-function mutations in the type III receptor tyrosine kinases KIT and PDGFRα a targeted treatment with the tyrosine kinase inhibitor imatinib was introduced and became the gold standard in advanced GIST disease. The success of this therapy with response rates of >80% stable disease and partial remission is still unmatched. Since then, many groups aim to identify other potential molecular targets. Genomic and proteomic signatures may pinpoint potential areas of interest for diagnostic tools, prediction of clinical outcome and potential response to therapeutic targets. This article gives an overview of the most important genomic aberrations in sarcomas, their differential diagnosis and the relevance of molecular biology for treatment strategies.

introduction

The histopathologic diagnosis of soft tissue tumours (STTs) is challenging for pathologists as STTs are rare compared with epithelial tumours. Sarcomas account for ∼1% of all malignancies. According to the current WHO classification from 2002 [1] >70 different entities exist that are more or less well characterized and defined. The single pathologist diagnoses a sarcoma rather rarely, thus lacking the experience as in more frequent tumour entities. In contrast to more frequent tumour entities, sarcomas are prone to be sent for a second opinion to a reference pathologist. This procedure is further warranted as the majority of spindle cell tumours require not only immunohistochemistry but subspecialty expertise and an increasing number of molecular methods to classify the different sarcoma subtypes. On one hand these molecular genetic changes underline differences between different sarcoma subgroups, on the other hand they may lead to the fusion of formally separated entities. The importance of correct classification of a soft tissue tumour is increasingly recognized to allow appropriate treatment. Furthermore, molecular signatures may pinpoint potential areas of interest for diagnostic tools, prediction of clinical outcome and potential response to therapeutic targets.

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In general, sarcomas can be subdivided into two morphological subgroups: tumours with a non-pleomorphic morphology and those with a pleomorphic phenotype. Additionally, these two groups can be further differentiated into sarcomas with specific molecular aberrations and those lacking such specific events.

This article provides an overview of the criteria on which the diagnosis of soft tissue tumours is based and points out which diagnostic tools are indispensable in sarcoma diagnosis and for treatment decisions (Table 1, adopted from Mertens et al. [2]).

specific reciprocal translocations in soft tissue sarcomas

The occurrence of a specific translocation occurs early in pathogenesis of soft tissue tumours. Two major genes involved in sarcomas are EWSR1 and the FUS gene [3–5]. Both genes encode RNA-binding proteins. The type of DNA-binding domain originating from the fusion partners probably determines the tumour type that results from the translocation. The resulting fusion proteins act as aberrant transcription factors that influence the cell cycle and processes such as apoptosis, angiogenesis, invasion and metastatic spread.

Sarcomas with involvement of the EWS1R gene locus are Ewing sarcoma [6], clear cell sarcoma [7], desmoplastic small

Table 1. Characteristic chromosome aberrations in soft tissue sarcomas

Tumour entity	Translocation	Fusion gene
Ewing sarcoma	t(11;22)(q24;q12)	*EWS1R–FLI1*
	t(21;22)(q22;q12)	*EWS1R–ERG*
	t(7;22)(p22;q12)	*EWS1R–ETV1*
	t(17;22)(q12;q12)	*EWS1R–E1AF*
	t(2;22)(q33;q12)	*EWS1R–FEV*
	t(16;21)(p11;q22)	*FUS–ERG*
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS1R–ATF1*
	t(2;22)(q33;q12)	*EWS1R–CREB1*
Desmoplastic small round cell tumour	t(11;22)(p13;q12)	*EWS1R–WT1*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWS1R–CHN*
	t(9;17)(q22;q11)	*TAF2N–CHN*
	t(3;9)(q12;q22)	*TFG–NR4A3*
	t(9;17)(q22;q11)	*TCF12–NR4A3*
Myxoid liposarcoma	t(12;16)(q13;p11)	*FUS–DDIT3*
	t(12;22)(q13;q12)	*EWS1R–DDIT3*
Solitary fibrous tumour/ haemangiopericytoma	der(12)(q13–15)	unknown
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	*TLS–ATF1*
	t(2;22)(q33;q12)	*EWS1R–CREB1*
	t(12;22)(q13;q12)	*EWS1R–ATF 1*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3–FOXO1A*
	t(1;13)(p36;q14)	*PAX7–FOXO1A*
	t(2;2)(p23;q36)	*PAX3–NCOA1*
	t(X;2)(q13;q36)	*PAX3–FOXO4*
Synovial sarcoma	t(X;18)(p11;q11)	*SS18–SSX1*
	t(X;18)(p11;q11)	*SS18–SSX2*
	t(X;18)(p11;q11)	*SS18–SSX4*
	t(X;20)(p11;q13)	*SS181–SSX1*
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13) der(22)t(17;22) ring chromosome	*COL1A1–PDGFB*
Congenital fibrosarcoma	t(12;15)(p13;q25)	*ETV6–NTRK3*
Inflammatory myofibroblastic tumour	t(2p23)	div. *ALK* fusion partners
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPSCR1–TFE3*
Endometrial stromal sarcoma	t(7;17)(p15;q21)	*JAZF1–JJAZ1*
Myxoinflammatory fibroblastic sarcoma	t(1;10)(p22;q24)	Deregulation of *FGF8 + NPM3*
	Ring chromosome	Amplification of *VGLL3*
Well differentiated liposarcoma/atypical lipomatous tumour	Ring chromosome/giant marker	Amplification of *MDM2*, *CDK4*, *HMGA2*, *GLI–SAS*
Low-grade fibromyxoid sarcoma	t(7;16)(q33–34;p11)	*FUS–CREB3L2*
	t(11;16)(p11;p11)	*FUS–CREB3L1*

round cell tumour [8], extraskeletal myxoid chondrosarcoma [9] and, rarely, angiomatoid fibrous histiocytoma [10]. The FUS gene is frequently involved in specific translocations of myxoid liposarcoma [11], angiomatoid fibrous histiocytoma [10] and less frequently in Ewing sarcoma.

Besides the possibility that the fusion product of a translocation acts as a transcription factor, this type of genomic alteration may lead to the autocrine stimulation of an involved receptor protein. This is, e.g. the case in dermatofibrosarcoma protuberans (DFSP) where the growth factor platelet-derived growth factor B (PDGFB) is placed under the control of the COL1A1 promoter [12]. Interestingly, this type of translocation can be targeted therapeutically with the very effective use of the tyrosine kinase inhibitor imatinib [13].

For diagnostic purposes, the involvement of both the EWS1R and the FUS genes can be detected by fluorescence *in situ* hybridization (FISH) using a break-apart probe. The principle of this break-apart assay is to use probes that hybridize to the gene locus on both sides of the breakpoint and which are labelled with different fluorophores (e.g. green and red). This leads to a split signal in the case of a translocation whereas an intact gene locus results in a fusion signal. Together with conventional morphology and immunhistochemistry the different tumour entities are easily distinguished although the second gene locus involved in the translocation is unknown.

A second common method of identifying specific translocations is the use of reverse transcription–polymerase chain reaction (RT–PCR). By choosing specific primers this method allows the identification of specific fusion products. Major disadvantages of RT–PCR are the possibility of false-negative results and the failure of amplification especially in formalin-fixed paraffin-embedded material.

specific somatic mutations and intragenic deletions in soft tissue sarcomas

This type of genomic alteration is well known from gastrointestinal stromal tumours (GISTs) where somatic mutations occur in either the *KIT* or the *PDGFRα* gene [14, 15]. By this finding, the pathogenesis of GISTs has been further elucidated. Shortly after the discovery of KIT mutations a very effective treatment was introduced with the application of tyrosine kinase inhibitors, namely imatinib (Glivec; Novartis, Switzerland) still being the first choice of treatment in advanced GIST disease [16–18]. Since the first description of these gain-of-function mutations, many efforts have been made to estimate the prognostic relevance of different types of mutation. The majority of studies were able to identify specific *KIT* mutations in exon 11 associated with a worse prognosis [19, 20], whereas *PDGFRα* mutations obviously correlate with a better outcome [21]. Furthermore, the type and location of mutations are predictive for treatment response to tyrosine kinase inhibitors and may even influence the dosage given [18].

There are now several examples in which soft tissue tumours present with an intragenic deletion or the loss of a whole gene. One is the rhabdoid tumour typically presenting in childhood

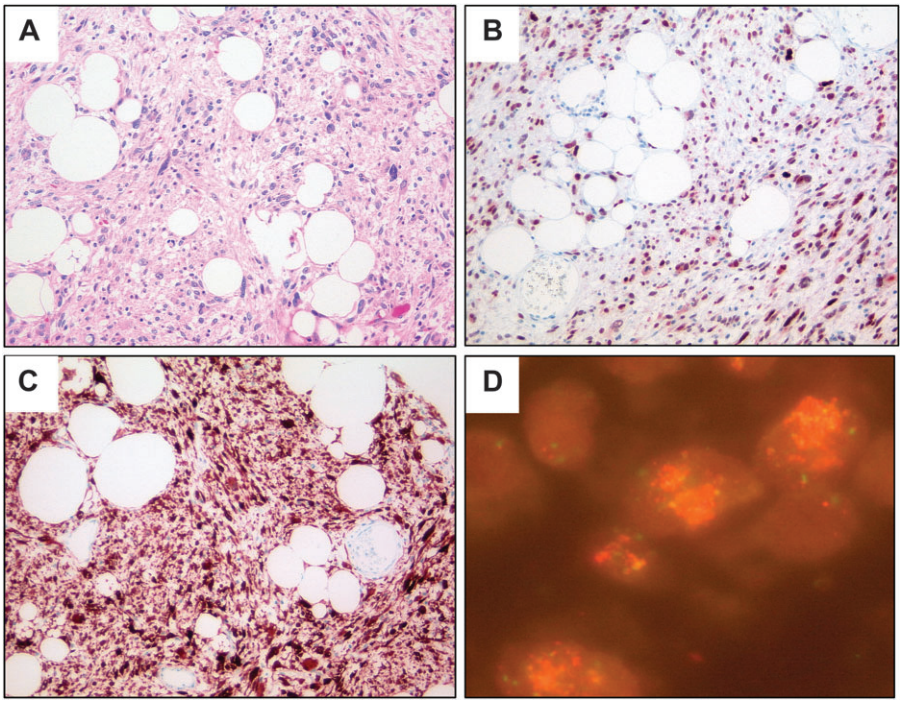

Figure 1. Dedifferentiated liposarcoma: (A) lipomatous and non-lipomatous areas (H&E stain); (B) with strong nuclear MDM2 expression and (C) strong positivity for CDK4 (original magnification ×100). (D) MDM2 amplification as shown by clusters of red signals and two normal green signals in the FISH analysis.

and rarely in young adults. Rhabdoid tumours are highly aggressive, associated with a poor prognosis and may be located either in the central nervous system or peripherally. They are characterized by the partial or complete loss of the *hSNF5/INI1* gene as result of point mutations leading to frameshifts, premature stop codons or deletions. The vast majority of tumours show an additional partial or complete loss of the wild-type allele resulting in a homozygous status. INI1 (hSNF5/SMARCB1) is located on chromosome 22q11.2 and belongs to the SWI/SNF chromatin remodelling complex. At the protein level the loss of the *hSNF5/INI1* gene can be detected by the loss of the immunohistochemical INI1 expression, which together with the morphological features, is diagnostic [22].

Loss of INI1 expression can also be detected in both conventional and proximal-type epithelioid sarcomas, in 50% of malignant peripheral nerve sheath tumours and some myoepithelial carcinomas [23]. These tumour entities can be distinguished from rhabdoid tumours by their morphological, immunhistochemical and clinical features.

Other examples of gene loss resulting in soft tissue tumours are the spindle cell lipoma and the well-differentiated spindle cell liposarcoma. These tumours are characterized by the loss of the Rb-1 gene [24].

amplifications in soft tissue sarcomas

Amplifications of specific genomic regions are not entirely specific for a given sarcoma subtype. However, the amplification of MDM2 and CDK4 both located on chromosome 12q13–15 due to ring and giant marker chromosomes is highly characteristic for the atypical lipomatous tumour/well-differentiated liposarcoma and dedifferentiated liposarcomas [25]. Together with classic histomorphology it helps to recognize dedifferentiated liposarcomas and to differentiate them from other spindle cell sarcomas. The gene products can also be detected by immunhistochemistry (Figure 1) although FISH analysis seems to be more sensitive and specific [25]. One has to be aware that MDM2 and CDK4 amplifications may also occur in osteosarcomas, chondrosarcomas, leiomyosarcomas as well as a small subset of rhabdomyosarcomas. From the translational point of view, linking genetics and treatment, MDM2 could be a promising therapeutic target [26, 27].

complex karyotypes in soft tissue sarcomas

The majority of high-grade sarcomas lack specific genetic alterations. These include high-grade pleomorphic sarcomas (formerly malignant fibrous histiocytomas), myxofibrosarcomas and leiomyosarcomas. As a result, in these tumour entities diagnostic algorithms are ill defined. Furthermore, it still remains difficult to identify potential therapeutic targets [28].

differential diagnosis in sarcomas

The subclassification of sarcomas is based on clinical data such as age, localization and radiological findings. On the biopsy or resection, histomorphology, immunohistochemistry and molecular pathology represent different diagnostic steps that should be used sequentially. Most often, sarcomas with low nuclear polymorphism turn out to be tumours with specific translocations whereas highly pleomorphic tumours often

carry complex karyotypes. As consequence the immunohistochemical spectrum in these high-grade tumours is often heterogeneous and reproducible diagnostic algorithms are hard to define.

Based on histomorphology, different morphological subtypes can be distinguished: spindle cell tumours, epithelioid cell tumours and small blue round cell tumours. The group with spindle cell morphology includes leiomyosarcomas, dedifferentiated liposarcomas, rhabdomyosarcomas, fibrohistiocytic tumours, synovial sarcomas (monophasic subtype), fibrosarcomas, solitary fibrous tumours, GISTs and malignant peripheral nerve sheath tumours. In the majority of these cases, immunohistochemistry in helpful to guide the decision whether further molecular diagnostic steps are needed. In case of smooth muscle differentiation detection of an MDM2/CDK4 amplification allows the distinction between leiomyosarcoma and dedifferentiated liposarcoma [25]. Synovial sarcomas can be identified by detection of a translocation involving the SYT gene locus [29]. In GISTs, CD117, PKCtheta and DOG1 expression are the most characteristic immunohistochemical markers [30–32]. The diagnosis may be further supported by the detection of a *KIT* or *PDGFRA* mutation. Rhabdomyosarcomas are characterized by the nuclear expression of MyoD1 and/or myogenin [33]. The diagnosis of a malignant peripheral nerve sheath tumours may be challenging because often only a subgroup of tumour cells are positive for S-100 protein. Thus, malignant peripheral nerve sheath tumour remains to be a diagnosis of exclusion [34].

All of the above-mentioned tumours may also present with a more epithelioid or mixed phenotype. In these cases, true epithelial or mesothelial differentiation has to be ruled out by immunhistochemistry. In GISTs, epithelioid morphology is often associated with a PDGFRA mutation [35]. Especially, these tumours may lack CD117 expression so that the correct diagnosis may be missed. A mutation analysis may support the correct diagnosis in these cases [36].

Small blue round cell tumours are a heterogeneous group where molecular diagnostic tools may be of special help. The group of Ewing sarcomas/primitive neuroectodermal tumours as well as the desmoplastic small round cell tumours is characterized by translocations involving the EWS or rarely the FUS gene locus. These translocations can be detected easily by using a break-apart FISH strategy. This also allows the distinction from other sarcomas with possible small-cell morphology such as synovial sarcoma while immunhistochemical marker profiles may overlap.

targeted treatment in sarcomas

In the last decade, the most impressive therapeutic effect in solid tumours has been reached with the use of the receptor tyrosine kinase inhibitor imatinib in GISTs. Since the first patient with advanced GIST disease has been treated successfully in 2001 by Joensuu [16], several worldwide studies have proved the efficacy of targeted treatment with 'small molecules' [18, 37]. During the past few years a large number of novel substances have been tested to achieve comparable results in other mesenchymal tumours. Although the translocation in the superficially located DFSP leading to fusion of PDGFB and COL1A1 was detected already in 1998 [38] (Figure 2) and thus in the same year as *KIT* mutations in GISTs [14] it took several years longer to test imatinib in this tumour entity. Rutkowski et al. [13] showed that this treatment helps to reduce the size and extension of previously inoperable cases. Unfortunately, until now no other sarcomas besides GIST and DFSP have been identified as regressing to a comparable extent.

Another interesting potential target could be the insulin-like growth factor receptor (IGFR)/AKT/mTOR pathway, which is strongly expressed in pleomorphic sarcomas [39] and synovial sarcomas [40]. AKT/mTOR inhibitors are effective *in vitro* and in mouse models and have now been introduced into clinical trials [41]. Another interesting target could be the group of histone deacetylases, which are for example involved in gene silencing, e.g. in synovial sarcomas [42] and endometrial stromal sarcomas [43].

conclusions

Up to now, treatment in sarcomas has been restricted to conventional chemotherapy and radiotherapy. Due to increasing molecular data from expression profiling and other molecular techniques, differential diagnosis and subgrouping of sarcomas has been facilitated. Novel targeted treatment regimens should be developed on the basis of these results. In clinical trials, elaborate subtyping of sarcomas is needed before randomizing patients and to identify responsive subgroups.

High-throughput sequencing is of great help in identifying of novel targets and is further supported by new applications such as RNA sequencing and characterization of epigenetic mechanisms. By these strategies, successful target-defined treatment comparable to the approach in GISTs should be the goal.

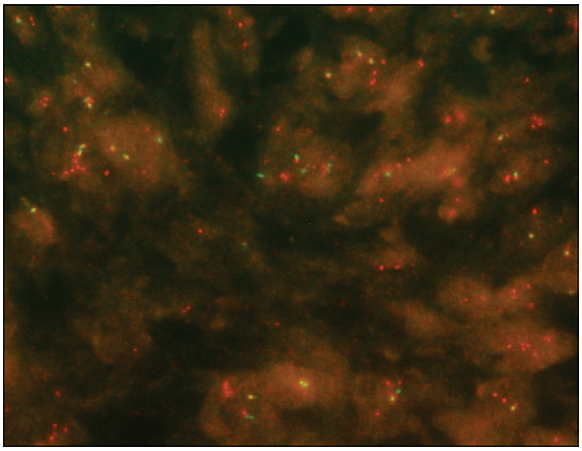

Figure 2. Dermatofibrosarcoma protuberans. FISH analysis using a custom designed break-apart probe to the PDGFB locus on chromosome 22q13 shows several tumour cells with one or two red–green signals indicating a normal chromosome 22 and three to six extra copies of the red signal indicating COL1A1–PDGFB gene fusion (original magnification ×1000).

disclosures

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