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Molecular biology of sarcoma

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ABSTRACT

Soft tissue sarcomas are a large group of heterogenous neoplasms, many of them are highly aggressive. Most of the cases are sporadic, without any well-defined pathogenetic factor. Potential risk factors are ionizing radiation, lymphatic oedema (secondary angiosarcoma of the breast), viral infections (HHV8 and Kaposi sarcoma), exposure to chemical factors (vinyl chloride and hepatic angiosarcoma). Genetic susceptibility plays a role in a minority of cases. However, mutations in *TP53*, *ATM* and *ATR* genes are associated with enhanced susceptibility to radiation. Li-Fraumeni syndrome (autosomal dominant *TP53* mutation) predisposes to development of malignancies, one third of them are sarcomas. Genetic alterations observed in sarcomas could be divided into three major groups characterized by: (1) chromosome translocations; (2) simple karyotype and mutations; (3) variably complex karyotypes. A large part of sarcomas belong to the first group and the specific chromosal translocations could be utilized in the diagnostic process. A smaller number of sarcomas could be assigned to the second group, e.g. desmoid fibromatosis (*CTNNB1* or *APC* mutations) and GIST (*KIT*, *PDGFRA*, or less frequently *BRAF*, *SDH*, *NF1*). A large number of sarcomas are characterized by complex and variable karyotypes. Gene copy number alterations are frequent in this group, e.g. in well-differentiated liposarcoma there is an amplification of *MDM2*, *CDK4* and *HMGA2* genes or sarcoma-specific chromosomal break regions present in the *CHOP* gene in myxoid liposarcoma and *FKHR* in alveolar rhabdomyosarcoma.

Key words: sarcoma, genetics, STS

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Soft tissue sarcomas account for a large group of heterogeneous mesenchymal tumours, which constitute about 1% of solid tumours in adults. Many of them are very aggressive, so they are responsible for disproportionately more malignancy-related deaths in young adults than cancers. Their typical classification is based on the similarity to healthy mesenchymal tissues to which the type of specific sarcoma is the closest. The term soft tissue sarcoma includes more than 70 types, and primary sarcoma consists of 12 basic types, which differ in terms of pathological and clinical features [1, 2].

In the vast majority of cases, sarcomas occur sporadically, without a clearly defined factor underlying tumorigenesis. Possible risk factors include exposure to ionising radiation, lymphoedema (breast angiosarcoma), viral infections (HHV8 — Kaposi sarcoma), or exposure to chemical agents (vinyl chloride — liver angiosarcoma) [2]. Mutations in genes *TP53*, *ATM*, and *ATR* are associated with increased sensitivity to ionising radiation and subsequent development of sarcomas [3]. In 10% of patients with type 1 neurofibromatosis (*NF1*, mutation in the gene encoding neurofibromin 1) gastrointestinal stromal tumours (GIST) as well as malignant peripheral nerve sheath tumours (MPNST) develop. Li-Fraumeni syndrome (autosomal dominant mutation in the *TP53* gene encoding p53 tumour suppressor protein) predisposes to the development of malignant tumours, one third of them are sarcomas. Other syndromes that predispose to the development of sarcomas are Gardner syndrome (desmoid tumour), Werner syndrome (soft tissue sarcomas), Bloom's syndrome (osteosarcoma), Beckwith-Wiedemann syndrome (rhabdomyosarcoma), and Costello syndrome (rhabdomyosarcoma). Some of the spindle cell sarcomas (SCSs) are present during the

course of other diseases, for example osteosarcomas during Paget's disease or chondrosarcomas during multiple cartilage-capped bony excrescences [2, 4–6].

Recent studies on a group of 1162 patients with sarcomas suggest other genetic risk factors, such as *BRCA2*, *ATM*, *ATR*, and *ERCC2* gene damage [3]. The early phase research centre MD Anderson Cancer Centre carried out an analysis of potential mutations in patients with soft tissue sarcomas, i.e. 102 consecutive patients directed to this centre were tested using the Foundation Medicine (FoundationOne) test based on next-generation sequencing (NGS). The study included a panel of 315 genes for which targeted drugs are established. Most commonly the mutations were found in *TP53* (31.4% of patients), *CDK4* (23.5%), *MDM2* (21.6%), *RB1* (18.6%), and *CDKN2A*/*B* (13.7%) genes. Interestingly, 50% of patients receiving treatment based on the result of the test (16%) achieved stable disease (SD). Of the 102 patients in the examined cohort, 40 (39%) were characterised by either no known mutation (7%) or no mutation currently recognised as the target of the available drug (32%). The remaining 62 (61%) patients had mutations potentially allowing the use of targeted therapy. Fourteen (14%) patients had lesions that could be used for treatment with the medicinal products registered for sarcoma treatment. There were cases of treatment with pazopanib or imatinib, which included five patients with the *PDGFR* mutation (1 GIST), four with the *FGFR* mutation, three with the *KIT* mutation (2 GIST), and two with the *KDR* gene aberrations [7]. Due to the high heterogeneity of sarcomas one should expect a very wide spectrum of genome damage but also numerous epigenetic changes.

Generally, the genetic changes observed in sarcomas can be divided into three groups:
— chromosomal translocations;
— point mutations without changing the karyotype;
— the presence of a variable and complex karyotype;

The sarcomas characterised by the presence of the first group of lesions (translocations) include a significant proportion of sarcomas. Occurrence of translocations is used for diagnostic purposes (Tables 1, 2). A smaller number of cases could be included in the group of the second type of defects (point mutations), for example desmoid tumour (*CTNNB1* or *APC* gene mutations) or GIST (*KIT* or *PDGFRA* mutations, significantly less *BRAF, SDH, NF1*). Finally, a large proportion of sarcomas are classified as the third type of lesion, which are characterised by a complex and variable karyotype. In these tumours, the number of gene copies may be much higher, such as in differentiated liposarcomas, in which the amplifications of the *MDM2*, *CDK4*, and *HMGA2* genes are observed. Typical chromosomal damage can also occur, such as in CHOP gene in myxoid liposarcoma and *FKHR* gene in alveolar rhabdomyosarcoma.

Recently published genomic research of the Cancer Genome Atlas Research Network (https://cancergenome.nih.gov/) [8] included a genetic analysis of 206 tumours of six major types of adult sarcomas. There were five tumours with complex karyotype: (1) dedifferentiated liposarcoma (DDLPS), (2) leiomyosarcoma (LMS), (3) undifferentiated pleomorphic sarcoma (UPS), (4) myxofibrosarcoma (MFS), (5) malignant peripheral nerve sheath tumour and sarcoma with a relatively simple karyotype, and (6) synovial sarcoma, in which a single chromosomal translocation t(X;18)(p11;q11) is typically observed. In contrast to tumours of epithelial origin, the examined sarcomas (with the exception of synovial sarcoma) are characterised primarily by changes in the number of gene copies, with a small overall number of point mutations (insertions, deletions, missense mutations). A high number of mutations occur in only a few genes (*TP53*, *ATRX*, *RB1*), which are "repeated" in many types of sarcomas. For example, while *MDM2* amplification was present in all DDLPS, deletions in *TP53* were found in 9% of LMS, 16% of UPS, and 12% of MFS. In RB path, *RB1* deletions were detected in 14% of LMS, 16% of UPS, and 24% of MFS; and *CDKN2A* deletions (p16) in 8% of LMS, 20% of UPS, and 18% of MFS. The disturbances of the RB pathway also included *CDK4* amplification in 86% and *CDKN2A* deletions in 2% of DDLPS. Generally, it has been shown that the total number of somatic mutations in the aforementioned types of sarcomas are relatively low (1.06 per Mb); however, 67% of tumours carried mutations previously known as potentially oncogenic. The highest mutation burden was identified in DDLPS and MPNST, mostly C>T mutations in the CpG islands. Only 12% of the tumours had elongated telomeres. A significant role in tumour progression of sarcomas may be played by specific changes in the DNA methylation pattern and regulation via miRNA. In these studies, *JUN* gene amplification was identified as a potential marker for shorter survival and a putative therapeutic target in the subgroup of DDLPS sarcomas. Although it has been found that uterine LMS (ULMS) and soft tissue LMS (STLMS) are molecularly distinct, inhibitors of the PI3K-AKT-mTOR signalling pathway may have potential application in the treatment of both sarcoma groups. STLMS were characterised by the activation of the *HIF1a* and *IGF1R* pathway, cell cycle (*CCNE2 — G1/S-Specific Cyclin-E2*), DNA replication (*MCM2* — minichromosome maintenance complex component 2), and DNA repair (*FANCI* — Fanconi anaemia group I protein) deregulation, while ULMS were mainly affected by DNA repair (*ESR1* — oestrogen receptor 1) disturbances. Finally, molecular analyses have shown that UPS and MFS are tumours with the same cellular origin (a common type of progenitor cell) that have different numbers of mucosal components,

Table 1. Genetic fusions in soft tissue sarcoma (modified, reprinted with permission from Sbaraglia and Dei Tos [2])

Sarcoma type	Genes	Chromosomal aberrations
Lipoma	*EBF1-LOC204010*	t(5;12)(q33;q14)
	HMGA2-CXCR7	t(2;12)(q37;q14)
	HMGA2-EBF1	t(5;12)(q33;q14)
	HMGA2-LHPF	t(12;13)(q14;q13)
	HMGA2-LPP	t(3;12)(q28;q14)
	HMGA2-NFIB	t(9;12)(p22;q14)
	HMGA2-PPAP2B	t(1;12)(p32;q14)
	HMGA2-LPP	t(3;6)(q27;p21)
	LPP-C12orf9	t(3;12)(q28;14)
Lipoblastoma	*COL1A2-PLAG1*	t(7;8)(q21q12)
	HAS2-PLAG1	Del(8)(q12q24)
	PLAG1-RAD51L1	t(8;14)(q12;q24)
	COL3A1-PLAG1	t(2;8)(q31;q12.1)
Chondroid lipoma	*C11orf95-MKL2*	t(11;16)(q13;p13)
Myxoid/round liposarcoma	*FUS-DDIT3*	t(12;16)(q13;p11)
	EWSR1-DDIT3	t(12;22)(q13;q12)
Soft tissue angiofibroma	*AHRR-NCOA2*	t(5;8)(p15;q13)
	GTF2I-NCOA2	t(7;8;14)(q11;q13;q31)
Dermatofibrosarcoma protuberans	*COL1A1-PDGFB*	t(17;22)(q21;q13)
Low-grade fibromyxoid sarcoma	*FUS-CREB3L2*	t(7;16)(q34:p11)
	FUS-CREB3L1	t(7;16)(p11;p11)
	EWSR1-CREB3L1	t(11;22)(p11;q12)
Solitary fibrous tumour	*NAB2-STAT6*	inv(12)(q13q13)
Infantile fibrosarcoma	*ETV6-NTRK3*	t(12;15)(p13;q25)
Sclerosing epithelioid fibrosarcoma	*FUS-CREB3L2*	t(7;16)(q34:p11)
	FUS-CREB3L1	t(11;16)(p13;p11)
	EWSR1-CREB3L1	t(11;22)(p11;q12)
Myxoinflammatory fibroblastic sarcoma/haemosiderotic fibrolipomatous tumour	*MGEA5-TGFBR3*	der(10)t(1;10)(p22;q24)
Inflammatory myofibroblastic tumour	*CARS-ALK*	t(2;11)(P23;P15)
	SEC31A-ALK	t(2;4)(P23;Q21)
	ATIC-ALK	inv(2)(P23;q35)
	RANBP2-ALK	t(2;2)(p23;q13)
	CLTC-ALK	t(2;17)(p23;q23)
	TPM3-ALK	t(1;2)(q21;p23)
	TPM4-ALK	t(2;19)(p23;p13)
	PPFIBP1-ALK	t(2;12)(p23;p11)
	RREB1-TFE3	t(X;6)(p11;p24)
Myxofibrosarcoma	*KIAA2026-NUDT11*	t(9;X)(p24;p11)
	CCBL1-ARL1	t(9;12)(q34;q23)
	AFF3-PHF1	t(2;6)(q12;p21)
Tenosynovial giant cell tumour	*COL6A3-CSF1*	t(1;2)(p13;q37)
Pericytoma with (7;12) translocation	*ACTB-GLI1*	t(7;12)(p22;q13)
Alveolar rhabdomyosarcoma	*PAX3-FOXO1*	t(2;13)(Q35;Q14)
	PAX7-FOXO1	t(1;13)(p36;q14)
	PAX3-FOXO4	t(X;2)(q13;q36)
	PAX3-NCOA1	t(2;2)(p23;q36)
	PAX3-NCOA2	t(2;8)(q36;q13)
	FOXO1-FGFR1	t(8;13;9)(p11;q14;q32)
Spindle cell rhabdomyosarcoma	*SRF-NCOA2*	t(6;8)(p21;q13)
	TEAD1-NCOA2	t(8;11)(q13;p15)
Angiomatoid fibrous histiocytoma	*EWSR1-CREB1*	t(2;22)(q33;q12)
	FUS-ATF1	t(12;16)(q13;p11)
	EWSR1-ATF1	t(12;22)(q13;q12)

→

Table 1 (cont.). Genetic fusions in soft tissue sarcoma (modified, reprinted with permission from Sbaraglia and Dei Tos [2])

Sarcoma type	Genes	Chromosomal aberrations
Ossifying fibromyxoid tumour	*EP400-PHF1*	t(6;12)(p21;q24)
	MEAF6-PHF1	t(1;6)(p34;p21)
	ZC3H7B-BCOR	t(X;22)(p11;q13)
Myoepithelioma/mixed tumour	*EWSR1-ATF1*	t(12;22)(Q13;q12)
	EWSR1-PBX1	t(1;22)(q23;q12)
	EWSR1-POU5F1	t(6;22)(p21;q12)
	EWSR1-ZNF444	t(19;22)(q13;,q12)
	EWSR1-KLF17	t(1;22)(p34.1;q12)
	EWSR1-PBX3	t(9;22)(q12.2;q33.3)
	FUS-KLF17	t(1;16)(p34.1;p11)
	LIFR-PLAG1	t(5;8)(p13;q12)
	SRF-E2F1	t(20;6)(q11;p21)
Clear cell sarcoma	*EWSR1-ATF1*	t(12;22)(q13;q12)
	EWSR1-CREB1	t(2;22)(q33;q12)
	IRX2-TERT	del(5)(p15.33)
Synovial sarcoma	*SS18-SSX1*	t(X;18)(p11;q11)
	SS18-SSX2	t(X;18)(p11;q11)
	SS18-SSX4	t(X;18)(p11;q11)
	SS18L1-SSX1	t(X;20)(p11;q13)
Biphenotypic sinonasal sarcoma	*PAX3-MAML3*	t(2;4)(q35;q31.1)
	PAX3-NCOA1	t(2;2)(q35;p.23)
	PAX3-FOXO1	t(2;13)(q35;q14)
Alveolar soft part sarcoma	*ASPSCR1-TFE3*	t(X;17)(p11;q25)
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3*	t(9;22)(q31;q12)
	TAF15-NR4A3	t(9;17)(q31;q12)
	TFG-NR4A3	t(9;3)(q31;q12)
	TCF12-NR4A3	t(9;15)(q31;q21)
	HSPA8-NR4A3	t(9;11)(q31;q24)
Desmoplastic small round cell tumour	*EWSR1-WT1*	t(11;22)(p13;q12)
Ewing sarcoma and Ewing-like sarcomas	*EWSR1-FLI1*	t(11;22)(q24;q12)
	EWSR1-ERG	t(21;22)(q22;q12)
	FUS-ERG	der(21)t(16;21)
	EWSR1-ETV1	t(7;22)(p21;q12)
	EWSR1-ETV4	t(17;22)(q21;q12)
	EWSR1-FEV	t(2;22)(q35;q12)
	EWSR1-NFATC2	t(20;22)(q13;q12)
	EWSR1-PATZ1	inv(22) (q12q12)
	EWSR1-SMARCA5	t(4;22) (q31;q12)
	EWSR1-POU5F1	t(6;22) (p21;q12)
	EWSR1-SP3	t(2;22)(q31;q12)
	FUS-FEV	t(2;16)(q35;p11)
	CIC-DUX4	t(4;19)(q35;q13)
	CIC-FOXO4	t(X;19)(q13;q13)
	BCOR-CCNB3	inv(X)(p11.4p11.22)
	FUS-NCATc2	t(16;20) (p11;q13)
Perivascular epithelioid cell tumours	*SFPQ-TFE3*	t(X;1)(p11;p34)
Soft tissue chondroma	*HMGA2-LPP*	t(3;12)(q28;214)
Mesenchymal chondrosarcoma	*HEY1-NCOA2*	del(8)(q13;q21)
	IRFBP2-CDX1	t(1;5)(q42;q32)
Epithelioid haemangioma	*ZFP36-FOSB*	t(19;19)(q13.32;q13.2)
Epithelioid haemangioendothelioma	*WWTR1-CAMTA1*	t(1;3)(p36;q25)
	YAP1-TFE3	t(x;11)(p11;q22)
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	*SERPINE1-FOSB*	t(7;19)(q22;q13)
Angiosarcoma	*CIC-LEUTX*	t(19;19)(q13.11;q13.2)

and their development can be driven by changes in the Hippo pathway [8].

Liposarcoma

Liposarcomas are divided into several subgroups that differ in clinical course and molecular perturbations. At present, liposarcomas are classified as well-differentiated, dedifferentiated, diversified, mucoid, round cell, and multiform.

Well-differentiated/atypical liposarcoma (WDLS)

Approximately 80% of atypical liposarcomas are characterised by the presence of additional ring or giant marker chromosomes that contain amplified material in the region 12q13-15. This fragment can have variable length and contains genes like *MDM2*, *TSPAN31*, *CDK4*, *HMGA2*, *CPM*, and *FRS2* [9]. The MDM2 and CDK4 proteins are involved in cell cycle regulation — MDM2 by binding to the p53 protein and inhibiting its function and CDK4 by stimulating the phosphorylation of the RB protein [9].

The 1q21-22 region including *COA*S and *PRUNE* oncogenes is also often amplified [10]. *PRUNE* is a negative regulator of the nm23-H1 metastasis suppressor protein, and its amplification leads to a decrease in the level of free nm23-H1 and subsequently increased proliferation and migration of cells [11]. Moreover, in some cases of WDLS co-amplifications of 12q21-22 were also observed [12].

Dedifferentiated liposarcoma (DDLS)

Dedifferentiated liposarcoma is considered to be a more aggressive form derived from well-differentiated liposarcoma, and it is similarly characterised by the presence of additional giant marker and ring chromosomes. DDLS is characterised by more copy number alterations (CNAs) than WDLS — 21% and 5.7%, respectively [13]. Among the numerous chromosome disorders, the most common is amplification of the 12q13-1 region containing the *MDM2* gene and a few rarer co-amplifications, among others 1q32 and 6q23, within which the *JUN* and *ASK1* genes are located [9, 14]. In the majority of cases where *MDM2* amplification is found, *p53* gene mutations are absent, which distinguishes dedifferentiated liposarcoma from other high-grade sarcomas [15]. It is also believed that activation of JUN signalling pathway may be involved in the progression of WDLS to DDLS [16].

An important mechanism involved in the dedifferentiation of WDLS into DDLS is the inhibition or complete blocking of adipogenesis in which *LIPE, PLIN*, and *PLIN2* genes are involved [17]. The expression level of genes associated with apoptosis (*BAX*, *BIRC5*, *SULF1*), cytoskeletal function (*CTNNB* 1, *MARKS*, *TMP4*, *PLEC*), Ras signalling pathway (*RAB23*, *HRASLS3*, *RAB20*), transcription factors (*TLE4*, *FOXF2*, *SOX11*), and cell cycle control *(MAPK1, CDC2*, *CCNB2)* differs significantly between DLLS and WDLS and may be involved in the dedifferentiation process [18].

Myxoid and round cell liposarcoma

The main chromosomal aberration in myxoid and round cell liposarcoma is t(12; 16)(q13; p11) translocation, which occurs in over 90% of cases [14, 19]. This translocation leads to fusion of *CHOP* (*DDIT3*) and *TLS* (*FUS*) genes located on chromosomes 12 and 16, respectively [20]. The presence of *TLS-CHOP* is a highly specific marker, not present in other subtypes of myxoid sarcomas [14]. The *CHOP* gene encodes a nuclear protein belonging to the C/EBP transcription factor family and is involved in the differentiation of adipocytes, erythropoiesis, and neoplastic transformation. The *TLS* gene encodes a nuclear RNA-binding protein that reacts with serine-arginine proteins involved in RNA splicing [14]. During the translocation, a joining of *TLS* gene transcription activating domain with the leucine zipper domain *CHOP* occurs. The resulting fusion protein leads to a change in the level of transcription of many genes, adipogenesis inhibition, and stimulation of cell proliferation resulting in tumour formation [21]. Due to the high homology of *TLS* and *EWS* genes, in rare cases (5–10%) a t(12; 22)(q13; q12) translocation is revealed, leading to *CHOP* and *EWS* gene fusions [22]. *TLS-CHOP* and *EWS-CHOP* translocations can be detected not only on the chromosomal level by FISH, but also at the transcript level using RT-PCR. To date, 11 variants of *TLS-CHOP* transcripts have been identified, the most common of which are type 2 (exon 5 *TLS* and 2 *CHOP*, approximately 66%), type 1 (exon 7 *TLS* and 2 *CHOP*), and type 3 (exon 8 *TLS* and 2 *CHOP*) [14, 23]. Furthermore, fusion mRNA can also be detected in the blood [24].

Apart from the specific gene fusions in 14–18% of MLPS cases activating mutation in *PIK3CA* gene or homozygous loss of *PTEN* gene are observed (the product of the latter is an inhibitor of the PIK3CA pathway). They lead to the activation of the PI3K/AKT signalling pathway and to excessive proliferation and increased cell invasiveness. A similar effect is observed in the case of overexpression of insulin-like growth factor type 2 (IGF2) and type 1 receptor (IGFR1) [25]. Telomerase reactivation observed in 39% of cases also contributes to MLS pathogenesis [26].

Table 2. Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
ALK	Translocation	Yes	*TPM3-ALK* fusion	t(1;2) (q22;p23)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase; participates in the development of the nervous system	The fusion leads to the formation of a constitutively active kinase	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*TPM4-ALK* fusion	t(2; 19) (p23; p13)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase; participates in the development of the nervous system	The fusion leads to the formation of a constitutively active kinase	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*CLTC-ALK* fusion	t(2; 17) (p23; q23)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*RANBP2-ALK* fusion	t(2; 2) (p23; q13)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*ATIC-ALK* fusion	t(2; 2) (p23; q35)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*CARS-ALK* fusion	t(2; 11) (p23; p15)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*SEC31L1-ALK* fusion	t(2; 4) (p23; q21)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*PPFIBP1-ALK* fusion	t(2; 12) (p23; p12)	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
ALK	Translocation	Yes	*RRBP1-ALK* fusion	?	Inflammatory myofibroblastic tumour	Receptor tyrosine kinase participates in the development of the nervous system	The exact mechanism of action is unknown; probably the fusion leads to the formation of a tyrosine kinase with increased activity	*ALK* translocations are present in 50% of IMT
APC	Mutation	Yes?	Point mutation/ /microdeletion	Various	Desmoid tumour	It controls the expression of beta-catenin	The function of the Wnt pathway is disrupted	10%
BCOR	Translocation	Yes	*BCOR- -CCNB3* fusion	Inv (X) (p11p11)	BCOR-rearranged sarcoma	It participates in the regulation of apoptosis routes	Perturbations in the programmed cell death pathway; dedifferentiation	NA

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
BCOR	Translocation	Yes	*BCOR--MAML3* fusion	?	BCOR-rearranged sarcoma	It participates in the regulation of apoptosis routes	Disorders in the programmed cell death pathway; dedifferentiation	NA
BCOR	Translocation	Yes	*ZC3H7B-BCOR* fusion	?	BCOR-rearranged sarcoma	It participates in the regulation of apoptosis routes	Disorders in the programmed cell death pathway; dedifferentiation	NA
BCOR	Translocation	Yes	*ZC3H7B-BCOR* fusion	t(X; 22) (p11; q13)	Endometrial stromal sarcoma, high grade	It participates in the regulation of apoptosis routes	Disorders in the programmed cell death pathway; dedifferentiation	NA
BRAF	Mutation	No?	Point mutation	V600	GIST	Serine-threonine kinase in the RAS/MAP	Increases the activity of the RAS/MAP pathway	Rarely
CCBL1	Translocation	No	CCBL1-ARL1	t (9; 12) (q34; q23)	Myxofibro-sarcoma	Kynurenine-oxoglutarate transaminase	The exact mechanism of action is unknown	NA
CDK4	Duplication	Yes	Amplification 12q13-15	Amplification 12q13-15	Dedifferentiated liposarcoma	Takes part in the control of the cell cycle	Promotes cell division	100%
CDX1	Translocation	No	IRFBP2-CDX1	t(1; 5) (q42; q32)	Mesenchymal chondrosarcoma	Transcription factor taking part among others in the development of the heart and intestines	The exact function unknown, perhaps contributes to oncogenesis by inhibiting the p53 protein	NA
CIC	Translocation	Yes	*CIC-DUX4* fusion	t(4; 19) (q35; q13) or t(10; 19) (q26; q13)	CIC-rearranged sarcoma	Transcriptional repressor; participates in the development of the central nervous system	Transition from the transcription repressor function to the factor that stimulates this process	NA
CIC	Translocation	Yes	*CIC-FOXO4* fusion	t(X; 19) (q13; q13.3)	CIC-rearranged sarcoma	Transcriptional repressor participates in the development of the central nervous system	Function unknown	Rarely
CSF1	Translocation	Yes	*CSF1-COL6A3* fusion	t(1; 2) (p13; q35)	Tenosynovial giant cell tumour	A factor that stimulates the formation of macrophage colonies	Overexpression of CSF1 causes massive infiltration of tumour mass by macrophages and its growth	25%
CTNNB1	Mutation	Yes?	Point mutation	T41A	Desmoid tumour	Encodes beta-catenin, a protein responsible for intercellular adhesion and participates in the Wnt signalling pathway	The function of the Wnt pathway is disrupted	85%
DDIT3 (CHOP)	Translocation	Yes	FUS-DDIT3 merger	t(12; 16) (q13; p11)	Myxoid liposarcoma	Proapoptotic transcription factor	Perturbations in the programmed cell death pathway	95%

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
DDIT3 (CHOP)	Translocation	Yes	EWSR1--DDIT3 merger	t(12; 22) (q13; q12)	Myxoid liposarcoma	Proapoptotic transcription factor	Disorders in the programmed cell death pathway	Rarely
EED	Mutation	No	Point mutation/ /microdeletion	EED inactivation	Malignant peripheral nerve sheath tumour	Takes part in the organisation of chromatin	It leads to increased activity of the RAS/MAP pathway	30%
EWSR1	Translocation	Yes	*EWSR1-ATF1* fusion	t(12; 22) (q13; q12)	Clear cell sarcoma	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	90%
EWSR1	Translocation	Yes	*CREB1-EWSR1* fusion	t(2; 22) (q32.3; q12)	Clear cell sarcoma	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	Rarely
EWSR1	Translocation	Yes	EWSR1-WT1 merger	t(11; 22) (p13; q12)	Desmoplastic small round cell tumour	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	75%
EWSR1	Translocation	Yes	*EWSR1-FLI1* fusion	t(11; 22) (q24; q12)	Ewing sarcoma/PNET	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor that stimulates cell division, perhaps less active than other mutations in ESFT	85%
EWSR1	Translocation	Yes	EWSR1-ERG merger	t(21; 22) (q12; q12)	Ewing sarcoma/PNET	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	10%
EWSR1	Translocation	Yes	EWSR1-ETV1	t(7; 22) (p24; q12)	Ewing sarcoma/PNET	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	Rarely
EWSR1	Translocation	Yes	EWSR1-E1AF	t(17; 22) (q12; q12)	Ewing sarcoma/PNET	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	Rarely
EWSR1	Translocation	Yes	FEV-EWSR1	t(2; 22) (q33; q12)	Ewing sarcoma/PNET	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	Rarely
EWSR1	Translocation	Yes	*EWSR1--CREB3L1* fusion	t(11; 22) (p11; q12)	Sclerosing epithelioid fibrosarcoma	The exact function is unknown; it encodes a protein binding to RNA	Chimeric transcription factor	90%

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
FOSB	Translocation	Yes	*SERPINE1*--*FOSB* fusion	t(7; 19) (q22; q13),	Pseudomyogenic haemangio-endothelioma	It takes part in dimerisation with the JUN family protein, leading to the formation of a transcription factor regulating cell division and differentiation	It leads to overexpression of FOSB	NA
FUS	Translocation	Yes	FUS-*CREB3L1*	t(11; 16) (p13; p11)	Sclerosing epithelioid fibrosarcoma	Takes part in DNA repair processes	Chimeric transcription factor, as a result of its action, the expression of genes controlled by *CREB3L1* is disturbed	Rarely
FUS	Translocation	Yes	*FUS-CREB3L2* fusion	t(7; 16) (q33; p11)	Sclerosing epithelioid fibrosarcoma	Takes part in DNA repair processes	Chimeric transcription factor, as a result of its action, expression of genes controlled by *CREB3L2* is disturbed	Rarely
FUS	Translocation	Yes	*FUS-CREB3L2* fusion	t(7; 16) (q33; p11)	Fibromyxoid sarcoma, low grade	Takes part in DNA repair processes	Chimeric transcription factor, as a result of its action, the expression of genes controlled by *CREB3L1* is disturbed	50%
FUS	Translocation	Yes	FUS-*CREB3L1*	t(11; 16) (p11; p11)	Fibromyxoid sarcoma, low grade	Takes part in DNA repair processes	Chimeric transcription factor, as a result of its action, expression of genes controlled by *CREB3L2* is disturbed	Rarely
GLI	Translocation	No	GLI-ACTB	t(7; 12) (p22; q13-15)	Pericytoma	Encodes the effector protein in the Hedgehog signalling pathway	Overexpression of the GLI factor	NA
HEY1	Translocation	Yes	HEY1--NCOA2 fusion	t (8; 8) (q13; q21)	Mesenchymal chondrosarcoma	A transcription factor induced by stimulation of the NOTCH pathway	It inhibits apoptosis, stimulates proliferation and the transition of cells from the epithelial to the mesenchymal form	80%
HMGA2	Duplication	No	Amplification 12q13-15	Amplification 12q13-15	Dedifferentiated liposarcoma	It participates in the differentiation of connective and fatty tissue	It leads to disorders in the differentiation of adipocytes	100%
IDH1	Mutation	Yes?	Point mutation	R132	Chondrosarcoma	It metabolises isocitrate to alpha-ketoglutarate in the Krebs cycle	It causes the transition of alpha-ketoglutarate to 2-hydroxyglutarate	21%
IDH2	Mutation	Yes?	Point mutation	R172	Chondrosarcoma	It metabolises isocitrate to alpha-ketoglutarate in the Krebs cycle	It causes the transition of alpha-ketoglutarate to 2-hydroxyglutarate	15%

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
IDH2	Mutation	Yes?	Point mutation	R140	Chondrosarcoma	It metabolises isocitrate to alpha-ketoglutarate in the Krebs cycle	It causes the transition of alpha-ketoglutarate to 2-hydroxyglutarate	Rarely
MBTD1	Translocation	Yes	*MBTD1*--*CXorf67* fusion	t(X; 17) (p11; q21)	Endometrial stromal sarcoma, low grade	The exact function is unknown; participates in embryonic development	The exact function is unknown; probably deregulates transcription processes by disrupting chromatin remodelling	Rarely
MDM2	Duplication	Yes	Amplification 12q13-15	Amplification 12q13-15	Dedifferentiated liposarcoma	It inhibits the action of p53 protein	It leads to a significant reduction in p53 activity	100%
NAB2	Translocation	Yes	*NAB2*--*STAT6* merger	Inv (12) (q13q13)	Solitary fibrous tumour	*NAB2* is a repressor of transcription; *STAT6* is its activator	As a result of gene fusions, a transcriptional activating protein is formed in regions usually inhibited by *NAB2*	55%
NCOA2	Translocation	No	SRF-NCOA2	t(6; 8) (p21; q13)	Spindle cell rhabdomyosarcoma	Transcription co-activator for many nuclear receptors; histone acetyltransferase activity	The exact mechanism is unknown; probably leads to a perturbation of gene expression responsible for the differentiation of muscle cells	NA
NCOA2	Translocation	No	TEAD1-NCOA2	t(8; 11) (q13; p15)	Spindle cell rhabdomyosarcoma	Transcription co-activator for many nuclear receptors; histone acetyltransferase activity	The exact mechanism is unknown; probably leads to a perturbation of gene expression responsible for the differentiation of muscle cells	NA
NF1	Mutation	No	Point mutation	NF1 inactivation	GIST	It negatively regulates the RAS/MAP kinase pathway	Disturbances in the functioning of neurofibromin 1 lead to increased activity of the RAS/MAP pathway	Rarely
NF1	Mutation	Yes	Point mutation/ /microdeletion	NF1 inactivation	Malignant peripheral nerve sheath tumour	It negatively regulates the RAS/MAP kinase pathway	Disturbances in the functioning of neurofibromin 1 lead to increased activity of the RAS/MAP pathway	88%
NR4A3	Translocation	Yes	*EWSR1*--*NR4A3* fusion	t(9; 22) (q22; q12)	Extraskeletal myxoid chondrosarcoma	Transcription factor participates in the control of cell division, differentiation and apoptosis	Modifies RNA post-translational processing	75%
NR4A3	Translocation	Yes	*TAF2N*--*NR4A3* fusion	t(9; 17) (q22; q11)	Extraskeletal myxoid chondrosarcoma	Transcription factor participates in the control of cell division, differentiation and apoptosis	The exact significance is unknown	Rarely

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
NR4A3	Translocation	Yes	*TCF12*--*NR4A3* fusion	t(9; 15) (q22; q21)	Extraskeletal myxoid chondrosarcoma	Transcription factor participates in the control of cell division, differentiation and apoptosis	The exact significance unknown	Rarely
NR4A3	Translocation	Yes	*TFG*--*NR4A3* fusion	t(3; 9) (q11; q22)	Extraskeletal myxoid chondrosarcoma	Transcription factor participates in the control of cell division, differentiation and apoptosis	The exact significance unknown	Rarely
NR4A3	Translocation	Yes	*RBP56*--*NR4A3* fusion	t(9; 17) (q22; q11)	Extraskeletal myxoid chondrosarcoma	Transcription factor participates in the control of cell division, differentiation and apoptosis	The exact significance unknown	20%
NTRK3	Translocation	Yes	*ETV6*--*NTRK3* fusion	t(12; 15) (p13; Q25)	Fibrosarcoma, neonatal form	Receptor tyrosine kinase; it promotes the survival and differentiation of neurons	It probactly leads to deregulation of the signal transduction in the *NTRK3* signal path	NA
NUDT11	Translocation	No	KIAA2026--NUDT11	t(9; X) (p24; p11)	Myxofibrosarcoma	Phosphatase	The exact mechanism of action is unknown	NA
PAX3	Translocation	Yes	*PAX3*--*FOXO1 (FKHR)* fusion	t(2; 13) (q35; q14)	Alveolar rhabdomyosarcoma	Transcription factor taking part among others in the development and differentiation of nervous and muscular tissue	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency; the differentiation towards muscle tissue is disturbed	75%
PAX3	Translocation	Yes	*PAX3*--*NCOA1* fusion	t(2; 2) (q35; p23)	Alveolar rhabdomyosarcoma	Transcription factor taking part, among others, in the development and differentiation of nervous and muscular tissue	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency	Rarely
PAX3	Translocation	Yes	*PAX3-AFX* fusion	t(X; 2) (q35; q13)	Alveolar rhabdomyosarcoma	Transcription factor taking part, among others, in the development and differentiation of nervous and muscular tissue	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency	Rarely
PAX3	Translocation	Yes	*PAX3*-MAML3	t(2; 4) (q35; q31.1)	Biphenotypic sinonasal sarcoma	Transcription factor taking part, among others, in the development and differentiation of nervous and muscular tissue	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency	79%

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
PAX3	Translocation	Yes?	*PAX3*-NCOA1	t(2; 2) (q35; p.23)	Biphenotypic sinonasal sarcoma	Transcription factor taking part, among others, in the development and differentiation of nervous and muscular tissue	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency	Rarely
PAX3	Translocation	Yes?	*PAX3*-FOXO1	t(2; 13) (q35; q14)	Biphenotypic sinonasal sarcoma	Transcription factor taking part, among others, in the development and differentiation of nervous and muscular tissue	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency	Rarely
Pax7	Translocation	Yes	*PAX7--FOXO1 (FKHR)* fusion	t(1; 13) (p36; q14)	Alveolar rhabdomyosarcoma	A transcription factor, highly homologous to *PAX3*	The fusion gene acts as a *PAX3*-like transcription factor, but with increased potency	10%
PDGFB	Translocation	Yes	*COL1A1--PDGFB* fusion	Ring form of chromosomes 17 and 22	Dermatofibrosarcoma protuberans	Isoform of platelet derived growth factor, essential in the process of angiogenesis	The fusion protein retains *PDGFB*-stimulating properties and stimulates tumour cells for development	75%
PDGFRA	Mutation	Yes	Point mutation	D842V	GIST	Receptor tyrosine kinase stimulation stimulates cells to grow and divide as a result of stimulation by platelet-derived growth factor	Constitutional kinase activation without the need for ligand	6%
PHF1	Translocation	Yes	*PHF1--JAZF1* fusion	t(6; 7) (p21; 7p15)	Endometrial stromal sarcoma, low grade	Takes part in the regulation of gene expression by changing the chromatin structure	The exact function is unknown; probably deregulates transcription processes by disrupting chromatin remodelling	50%
PHF1	Translocation	Yes	*EPC1-PHF1* fusion	t(6; 10) (p21; p11)	Endometrial stromal sarcoma, low grade	Takes part in the regulation of gene expression by changing the chromatin structure	The exact function is unknown; probably deregulates transcription processes by disrupting chromatin remodelling	Rarely
PHF1	Translocation	Yes	*MEAF6--PHF1* fusion	t(1; 6) (p34; p21)	Endometrial stromal sarcoma, low grade	Takes part in the regulation of gene expression by changing the chromatin structure	The exact function is unknown; probably deregulates transcription processes by disrupting chromatin remodelling	Rarely
PHF1	Translocation	No	AFF3-PHF1	t(2; 6) (q12; p21)	Myxofibrosarcoma	Takes part in the regulation of gene expression by changing the chromatin structure	The exact function is unknown; probably deregulates transcription processes by disrupting chromatin remodelling	NA

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
ROS1	Translocation	Yes	TFG-ROS1 merger	?	Inflammatory myofibroblastic tumour	A receptor tyrosine kinase with a similar structure to ALK; exact function unknown	The exact mechanism of action is unknown, probably the fusion leads to the formation of a tyrosine kinase with increased activity	Rarely
ROS1	Translocation	Yes	*YWHAE--ROS1* fusion	?	Inflammatory myofibroblastic tumour	A receptor tyrosine kinase with a similar structure to ALK; exact function unknown	The exact mechanism of action is unknown, probably the fusion leads to the formation of a tyrosine kinase with increased activity	Rarely
SDHB/ /SHDC/ /SDHD	Mutation	No	Point mutation	Various	GIST	Succinate dehydrogenase (SDH) subunit, an enzyme involved in the process of cellular respiration	SDH deficiency probably leads to oxidative stress and to increased stimulation of cell growth by IGF and VEGF	5%
SMARCB1	Translocation	Yes	*SMARCB1* inactivation	Delegation 22q	Rhabdoid tumour	Takes part in chromatin remodelling	The lack of activity of *SMARCB1* leads to dysregulation of the cell cycle	35%
SMARCB1	Translocation	Yes	*SMARCB1* inactivation	Delegation 22q	Epithelioid sarcoma	Takes part in chromatin remodelling	The lack of activity of *SMARCB1* leads to dysregulation of the cell cycle	Total 90–95%
SMARCB1	Translocation	Yes	*SMARCB1* inactivation	t(8; 22) (q22; q11)	Epithelioid sarcoma	Takes part in chromatin remodelling	The lack of activity of *SMARCB1* leads to dysregulation of the cell cycle	Total 90–95%
SMARCB1	Translocation	Yes	*SMARCB1* inactivation	t(10; 22)	Epithelioid sarcoma	Takes part in chromatin remodelling	The lack of activity of *SMARCB1* leads to dysregulation of the cell cycle	Total 90–95%
SS18	Translocation	Yes	SS18-SSX1	t(X; 22) (p11.23; q11)	Synovial sarcoma	Transcription factor	The exact function is unknown; it may interfere with cell differentiation by affecting epigenetic factors	60–70% monophasic, 30–40% biphasic
SS18	Translocation	Yes	SS18-SSX2	t(X; 18) (p11.21; q11)	Synovial sarcoma	Transcription factor	The exact function is unknown; it may interfere with cell differentiation by affecting epigenetic factors	97% monophasic, 3% biphasic
SS18	Translocation	Yes	SS18-SSX4	t(X; 18) (p11; q11)	Synovial sarcoma	Transcription factor	The exact function is unknown; it may interfere with cell differentiation by affecting epigenetic factors	Rarely
SS18L	Translocation	Yes	SS18L-SSX1	t(X; 20) (p11; q13)	Synovial sarcoma	Transcription factor	The exact function is unknown; it may interfere with cell differentiation by affecting epigenetic factors	Rarely

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Table 2 (cont). Mutations and translocations

Gene	Damage type	Diagnostic value	Genetic disorders	Description of the translocation or mutation	Tumour	The function of the wild-type gene	Mechanistic role	Incidence
SUZ12	Translocation	Yes	*JAZF1-SUZ12* fusion	t(7; 17) (p15; q21)	Endometrial stromal sarcoma, low grade	Participates in the regulation of embryonic development	It causes the constitutive expression of a chimeric protein with antiapoptotic properties	30%
SUZ12	Mutation	No	Point mutation/ /microdeletion	*SUZ12* inactivation	Malignant peripheral nerve sheath tumour	It participates in the regulation of embryonic development	It leads to increased activity of the RAS/pathway	50%
TFE3	Translocation	Yes	*TFE3-ASPSCR1* fusion	t(X; 17) (p11.2; Q25)	Alveolar soft part sarcoma	Both *TFE3* and *ASPSCR1* are transcription factors	As a result of translocation, a transient transcription factor that promotes oncogenesis is formed	99%
TFE3	Translocation	Yes	*YAP1-TFE3* fusion	t(X; 11) (p11; q22)	Epithelioid haemangio-endothelioma	Transcription factor	The exact significance unknown; the function of the Hippo pathway is probably disrupted	22%
WWTR1	Translocation	Yes	*WWTR1- -CAMTA1* fusion	t(1; 3) (p36; Q25)	Epithelioid haemangio-endothelioma	It participates in the control of the size of internal organs, a pro-apoptotic factor	The exact function is unknown	~55%
YWHAE	Translocation	Yes	*YWHAE- -NUTM2A* fusion	t(10; 17) (q22; p13)	Endometrial stromal sarcoma, high grade	A signalling protein from the family 14-3-3, probably involved in the regulation of cell division	The exact function is unknown	up to 26%

Pleomorphic liposarcoma (PLS)

The cytogenetic picture of pleomorphic liposarcoma is associated with the occurrence of aneuploidy with numerous chromosomal aberrations. The number of chromosomes in the cell may exceed 200, and within the tumour there may be a large heterogeneity of cells, which significantly hinders the identification of characteristic rearrangements [9]. Numerous amplifications are observed in the genetic profile, including 1p21, 1q21-22, 5p13-15, 7q22, 13q31-32, and 20q13. Mutations loss of function in *TP53* and *NF1* genes have also been described. *CCND1*, *CCND2*, *MYB*, *MDM2*, *GLI1*, and *CDK4* gene amplifications are present in PLS [27].

Leiomyosarcoma

Leiomyosarcomas are characterised by complex genetic perturbations and highly complex karyotypes with numerous losses and amplifications of multiple chromosomal regions. Available data are very complex and limited. Genomic hybridisation assays revealed that genetic perturbations in leiomyosarcomas encompass 2218 genes in 25 chromosomal regions [28]. The most common are losses within 10q, 13q14-21, and 19p regions [29–31]. Amplifications are most commonly found within 17p and also 5p15, 8q24, 15q25-26, and Xp [29]. It should be noted that the number of cytogenetic abnormalities increases with the size of the tumour [29], and this correlates negatively with the patients' survival [32].

Despite the fact that the 17p region in which the *TP53* gene is located is amplified, one of the main mechanisms underlying the development of leiomyosarcomas is the loss of tumour suppressor functions of p53 and Rb proteins. 19p deletion and loss of function of *p16INK* and *ARF* genes located there, which are important regulators of tumour suppressors RB and p53, are among the main mechanisms of inactivation of these genes [33]. The decrease of p16 expression may also result from methylation of *p16INK4* gene promoter [34].

The second important mechanism involved in the development of leiomyosarcoma is direct loss of the *RB* gene located in region 13q14.2-14.3 [31]. Moreover, in the amplified 17p11-12 region the *COPS3* gene is located, whose activation leads to increased degradation of p53 protein in proteasomes. Thus, amplification of *COPS3* is one of the mechanisms leading to inactivation of p53 [35]. In less common cases the loss of p53 protein function results from its inhibitor MDM2, which is overexpressed in more than 10% of leiomyosarcomas [36].

PI3K/Akt signalling pathway perturbations play an important role in pathogenesis, and they are overexpressed in many cases of leiomyosarcomas. The loss of the 10q region leads, among others, to the loss of the *PTEN* gene [29] — the negative regulator of this pathway [37]. Studies in animal models have shown that loss of *PTEN* function is an important, but insufficient element in the development of leiomyosarcoma [37]. It is believed that *PTEN* dysfunction also contributes to the development of genetic instability, and activation of the PI3K/Akt pathway increases the phosphorylation of Mdm2 protein and the loss of p53 protein function [38].

In the amplified 17p11.2 region the *MYCOD* gene is also located, which encodes a transcription factor specific for smooth muscle and cardiomyocytes, which regulates transcription of genes responsible for cell differentiation and migration [39]. The research indicates that perturbations of the DNA double-strand break repair mechanisms, resulting from the loss of *FANCA* and *BRCA1* gene function, are a potential mechanism involved in pathogenesis and a possible target of treatment with PARP inhibitors [38]. The genes potentially involved in the pathogenesis of leiomyosarcoma also include amplified *MYC*, *MYB, COPS3, GLI, CDK*4, *SAS, FLF*, and *PRUNE* genes [40].

Based on recent studies, leiomyosarcomas have been divided into three classes based on overexpression of certain markers. Type I is characterised by overexpression of *ACTG2*, *SLMAP*, *LMOD1*, *CFL2*, and *MYLK* genes, type II by overexpression of *ARL4C*, *CDK4*, *CTNNB1*, *AURKA*, *RHEB*, *EGFR, CCND1, MTO*R, *MAPK1, NOTCH2*, and *ROR2* genes, and type III by overexpression of *MDM4, ERB3, EPHA3, ESR1,* and *EGFR* genes and activation of pathways involved in metabolism, ion transport, and transcription regulation [41]. The role of individual pathways in the development of leiomyosarcoma requires deeper knowledge and further detailed research.

Synovial sarcoma

Synovial sarcoma (the name synovial is misleading because this tumour is not derived from synovial cells and does not express specific synovial markers; another name for this tumour is *synovioma malignum*) is a soft tissue tumour most commonly found in the lower limbs in young adults [42]. In the case of small tumours (< 5 cm), the prognosis is favourable, larger tumours are associated with a higher risk of metastasis and local recurrence [43].

The specific chromosomal aberration in synovial sarcoma is t(X;18) translocation, which is used for diagnostic purposes (using cytogenetic or RT-PCR methods) [44]. Synovial sarcoma is characterised by relatively small genetic complexity — almost half of primary tumours do not carry chromosomal aberrations other than t(X;18), while in other cases only a small number of lesions occur [45]. Changes in the number of chromosomes and

higher genetic complexity are more common in adults than in children [45]. Higher genetic complexity was observed in metastatic and recurrent tumours [46], it also correlated with a higher incidence of metastases and a shorter survival time [45].

Translocation t(X;18) causes the fusion of *SS18* gene (alternative name *SYT*, chromosome 18) with genes from the *SSX* family on X chromosome (*SSX1*, *SSX2*, or less often *SSX4*). SS18 protein and proteins from the SSX family regulate transcription, although they are not transcription factors in the strict sense — they do not have DNA binding domains. SS18 stimulates the transcription, and SSX proteins inhibit this process. It seems that the *SS18-SSX1* and *SS18-SSX2* fusion effects are slightly different. *SS18-SSX1* promotes proliferation, migration, and invasiveness of tumour cells, and *SS18-SSX2* affects the adhesion and cytoskeleton of tumour cells [42].

In contrast to other malignancies, due to the relative chromosomal stability in synovial sarcoma, mutations within the *TP53* gene are relatively rare. The unchanged p53 protein is found in the majority of synovial sarcomas, but its function can probably be altered, e.g. as a result of regulation by the AKT-PTEN pathway [47].

Epithelioid sarcoma

Epithelioid sarcoma is rare (less than 1% of all soft tissue sarcomas) and aggressive type of sarcoma occurring mainly in children and young adults. Although it is a tumour of mesenchymal origin, the cells have both mesenchymal and epithelial markers [48].

Epithelioid sarcoma can be divided into two subtypes: a distal (classic; most cases, lesions rather in the lower part of the body) and a proximal (lesions more in the upper body, including head and neck) with different histological characteristics. Distal epithelioid sarcoma is more common in younger patients (mean age of patients 29 years), with predominance in men. The proximal subtype is more common in older people (mean age of patients 40 years) [49].

In the vast majority of samples of this tumour, cells with very complex karyotype are observed, and only a small part of tumours have diploid or polyploid cells. Epithelioid sarcomas occurring in children have less complex karyotypes compared to malignancies found in adults. Translocations (8;22)(q22;q11) and t(10;22) were observed in distal and proximal epithelioid sarcoma, respectively. In most cases, the changes affect the longer arm of chromosome 22. Unlike other soft tissue sarcomas, epithelioid sarcoma cannot be distinguished by the unique cytogenetic pattern "characteristic" for this type of sarcoma [48].

Due to changes in the long arm of chromosome 22, a loss of *SMARCB1* expression is observed in most cases of both types of epithelioid sarcomas [50]. Immunohistochemistry showed a loss of *SMARCB1* expression in 85–93% of cases (depending on the source) [48]. Loss of expression occurs through various mechanisms, and a significant proportion may be gene silencing by miRNA, in particular by miR-765, an increased level of which appears to be specific for epithelioid sarcomas [51].

Gene *SMARCB1* (another name *INI1*) (22q11) encodes the BAF47 protein (SWI/SNF-related matrix-associated, actin-dependent regulator of chromatin subfamily B member 1), which is one of the subunits of the ATP-dependent complex of SWI/SNF remodelling chromatin. The components of this complex are mutated in a significant number of tumours, in particular in the malignant rhabdoid tumour [52]. BAF47 acts as a tumour suppressor, and its inactivation leads to neoplastic transformation resulting from deregulation of target gene transcription [48].

In the case of epithelioid sarcoma, inactivation of *SMARCB1* alone is not sufficient for neoplastic transformation. The *SMARCB1* knock-out in a fibroblast cell line caused growth arrest and activated apoptosis mediated by p53 [53]. Only the coexistence of the *SMARCB1* and *TP53* mutations caused a dramatic increase in proliferation [54]. It is also postulated that other proteins and signalling pathways contribute to tumour progression due to the complex genetic landscape of epithelioid sarcoma [48].

Ewing sarcoma

According to the World Health Organisation classification, Ewing sarcoma is referred to as a malignant tumour with uncertain differentiation [2]. It accounts for 6–8% of primary malignant bone tumours. It is a rare malignancy, occuring most often in populations of European origin, with a frequency of 1.5 cases per million children, adolescents, and young adults [55]. Ewing sarcoma most often appears in the second decade of life, and there is a characteristic translocation causing *EWSR1-ETS* fusion [6]. In most cases they are translocations of *EWS* and genes from *ETS* transcription factor family, in over 85% of cases with *FLI1*, in 10% with *ERG* [17]. The most frequent translocation is t(11;22)(q24;q12). The *EWSR* 1 gene is located at 22q12 and *FLI1* at 11q24. There are several variants of these translocations. Expression of the fusion protein in normal cells leads to their death, while in an undifferentiated or malignant cells it causes disorders of differentiation resulting in the development of malignancy [56, 57]. The effect of fusions between genes from the *EWS* and *ETS* families are new transcription factors that influence cellular processes related to proliferation, apoptosis, autophagy, and cell viability [17].

It is generally considered that tumours occurring in children have very stable genomes, any mutations of genes associated with signalling pathways or chromatin modifications are uncommon in paediatric Ewing sarcomas [58]. Mutations in three genes are found — loss of *STAG2* (15–17%), *CDKN2A* (12–22%), and *TP5* 3 (6–7%); however, those mutations in *STAG*2 and *CDKN2A* genes never occur together [58]. Loss of *STAG*2 expression (SA2 cohesin subunit) is associated with metastasis, so it could be the target of therapy [58]. However, the authors of this study point out that there are very few mutations in general, and besides the ones mentioned above, they are not repeated in different patients. There are some repeated abnormalities of chromosome numbers: an additional chromosome 8 in 50% of cases, slightly less (20–25%) chromosome 2 and chromosome 1q as well as chromosome 20 in 10–20% of cases. Additional chromosome 1q and probably loss of chromosome 16q have negative prognostic significance [55].

It is still uncertain from which cells this tumour is derived [55], but due to the presence of characteristic gene fusions in virtually all cases, it is a very good object to study. The possible original cells are neural crest cells and mesoderm cells, and Ewing sarcoma precursor cells have also been found to be enriched in embryonic osteochondrogenic progenitor cells [59].

Similarly to many other diseases, association studies were undertaken for a large sample of 733 cases and over 1300 control persons, and some loci predisposing to the occurrence of Ewing sarcoma were detected — among others in 6p25.1, 20p11.22, and 20p11.23. Moreover, this study confirmed the previously obtained associations for loci in three other places [60]. Due to the fact that there are several of these sites, and the rare occurrence of the disease, this has no prognostic value, but it may better explain the mechanism of disease formation.

Rhabdomyosarcoma

According to the World Health Organisation classification, rhabdomyosarcoma (RMS) is a malignant tumour of skeletal muscle [2]. They constitute 40% of soft tissue sarcomas in children, but only 3–4% of all malignancies in this age group [17], although maybe even 5–10% [61]. Determining the type of malignancy is extremely important because the survival rate is within the range 35–90%, depending on the subtype. Rhabdomyosarcomas are divided into several types; the most common of these are embryonal rhabdomyosarcomas (ERMS), occurring in about 60% of cases, and the next most common (20%) are alveolar rhabdomyosarcomas (ARMS), consisting of cells having characteristics of embryonic skeletal cells. For ARMS the translocations connecting *PAX3* or *PAX7* with *FOXO* are characteristic, leading to fusion gene formation [6], and in general are found in the majority of these tumours (77%) [17]. Changes in ERMS are more diverse — *CDKN2A*/*B* deletions (23%), *FGRF4* activating mutations (20%), *NF1* deletions (15%), mutations activating genes from the ras family (12–42%), and mutations in *FGFR4* (9%) and *PIK3C* A (5%). In addition, 31% of ERMS have high *GLII* expression [17]. In the same study it was stated that in RMS not otherwise specified mutation in the ras pathway occur in 35–45% of cases, and mutations in *TP53* in 5–22% and *MDM2* amplification in 10–17% of cases.

A small proportion of *ERMS* and ARMS accompany other genetic neoplastic diseases — among others Beckwith-Wiedemann syndrome, Werner's syndrome, and Noonan's syndrome [6, 62].

It is believed that mutations are detected in sarcomas less frequently than in cancers, although the data given above do not confirm that. This view may change with the currently intensively used genomic sequencing approach — studies conducted in 1162 patients with sarcomas showed that 66 had mutations in genes such as *TP53*, *BRCA2*, etc., and 25% had potentially pathogenic variants in one or more genes [3], but these data are given for different sarcomas. In contrast, mutations are observed in *TP3* for RMS, ERMS (*BRAF*, *CTNNB1*, *FGFR4*, *KRAS*), and for ARMS mentioned above as a result of chromosomal translocation fusion *Pax7*/*FOXO1* and *Pax3*/*FOXO1* [63]. These fusions occur between chromosomes 1 and 13 or 2 and 13, respectively. As a result of *PAX3-FOXO1* fusion, a strong transcriptional activator is formed; it is believed to contribute to the pathogenesis of ARMS by activating genes — among others *PDGFR* [17]. The list of genes whose expression is regulated by this fusion is long — there are over 200 of them [64].

However, additional changes in the genome are needed for tumorigenesis, including *MYCN*, *CDK4*, and *MIT17-02* amplification, *CDKN2A* deletion, or loss of heterozygosity in the 11p15.5 chromosome [17, 65]. In patients with ARMS without the above fusions, mutations in the *NRAS* and *PIK3CA* genes are present [17]. Furthermore, it has recently been found that in non-*PAX-FOXO* RMS, the *RAS* gene acting through the *RAF*-*MEK* pathway (*MAPK*/*ERK,* mitogen activated protein kinase/extracellular signal regulated kinase) inhibits the differentiation of rhabdomyosarcoma cells into muscle cells by repression of myogenic agent *MYOG*, needed for cell differentiation [66]. It is also known that the key regulator of ARMS growth is the SNAIL factor, which inhibits the expression of *MYF5* and *MYOD* transcription factors; in human myoblasts inhibition of SNAIL causes an increase in the level of factors favouring differentiation into muscle and may have potential therapeutic application [67].

There are increasing numbers of studies analysing molecular changes in RMS, including proteome and epigenetic changes, and it has recently been found that ARMS occurs in more differentiated cells than ERMS, and that in RMS not only *RAS /MEK/ERK/CDK4/6* pathway is deregulated, but there are also disorders in the so-called Unfolded Protein Response (pathway associated with the reaction to the accumulation of improperly folded proteins) and in mitosis between the G2 and M stage [68].

The nature of RMS seems complicated; recently 29 genes have been identified that affect the development of this malignancy. Both suppressors and so-called driver genes controlling tumour growth are associated with different cellular processes — apoptosis, cell adhesion, DNA repair, protein folding, response to oxidative stress, and others [69].

In patients with metastatic ARMS the four-year survival is much better (75%) for the *PAX7-FOXO1* fusion, but only 8% for the *PAX3-FOXO1* fusion [17].

In ERMS there is a loss of both alleles in the region of chromosome 11p15.5, in regions where a tumour suppressor or suppressors are located. There are also a variety of other changes in a number of chromosomal sites; in about 35% of cases there are also mutations in the *RAS* gene family [17, 70] and additional mutations in *TP53*, *MDM2*, *CDKN2A*, *GLI1*, *CTNNB1*, and *PRPN11* genes [17].

Undifferentiated pleomorphic sarcoma and myxofibrosarcoma

According to the World Health Organisation classification, myxofibrosarcoma (MFS) is referred to as a malignant fibroblastic/myofibroblastic tumour and undifferentiated pleomorphic sarcoma (UPS) as undifferentiated/unclassified sarcoma [2]. Tumours, such as undifferentiated pleomorphic sarcoma, do not have a clear pattern of differentiation or the normal tissue related to them is not known.

In alveolar soft tissue myxofibrosarcoma there was a rare occurrence of mutations in *NF1* and *TP53* genes [63].

In myxofibroma the following fusions are present: *KIAA2026-NUDT11*, *CCBL1-ARL1*, and *AFF3--PHF1* (t[9;X][p24;p11]; t[9;12][q34;q23]; t[2;6][q12;p21], respectively) [2].

Although these two types of malignancies will be discussed separately, it is justified to combine them in one chapter because the recently published genomic characteristics results for different sarcomas classify UPS and MFS as one group with a range of phenotypic differences [8]; these studies were extensive and included analyses of mRNA, microRNA, DNA sequences, methylation, and the number of individual gene copies. It was found that the genes associated with the matrix are expressed at a higher level in MFS. In 10% of cases, amplification of the gene *CCNE1* was found, whereas *VGLL3* was amplified in 11% of cases. They is interesting because the authors state that because these genes are related to the Hippo signalling pathway, so inhibitors of this pathway may be used in the therapy of MFS and UPS.

UPS is one of the most common sarcomas in older people; it is most common in patients between 50 and 70 years old, and rare in children. In general, tumours are located deeply, although recently a case of UPS with a skin location was also described [71]. The spectrum of mutations found in UPS has not been fully characterised; however, these tumour cells are quite similar to mesenchymal stem cells [72]. There are very few general studies on this malignancy, but the vast majority of literature consists of case reports.

Even the origin of these malignancies is not clear, because there is a suspicion that at least in some cases it may be a carcinoma and not a sarcoma. Moreover, because its classification is difficult due to the changing diagnostic criteria, these lesions are described, but this is not a homogeneous group. There are no characteristic changes for UPS, although the changes in chromosome number are frequent — both reduction and polyploidisation [73]. There are many different changes in individual regions of chromosomes, and region 12q13-15 seems to be particularly important.

In individual cases of more accurately tested UPS mutations in individual genes are detected — for example in *KRAS* and *PIK3CA* in one patient [74], but it is certainly not characteristic for all cases, not even for the majority, contrary to changes in chromosome number and the amplification of individual parts of the genome.

Due to the fact that these malignancies are poorly characterised, it is difficult to consider targeted therapy, but there are some attempts in this direction. Using earlier data on activated protein kinase B (AKT) in 20% of patients with UPS, overexpression of which was correlated with poor survival [75], it has been shown that it is possible to inhibit cellular proliferation *in vitro* from UPS by using a combination of IGF1R/PI3K/mTOR pathway inhibitors and an IGF1R kinase inhibitor [76].

Recently 95 patients with UPS were screened to find possible mutations that would allow targeted therapies [77]. This study showed that classification to UPS is quite often faulty — ultimately only 18 patients had UPS and 44 had MFS, and only in one patient with UPS a mutation allowing consideration of targeted therapy was detected (*PIK3CA* mutation) [77], so it seems that UPS is not a candidate for diagnostics based on sequencing the patients' genomes.

MFS is also common in older people. Cytogenetic studies have shown frequent amplification of the 5p

chromosome region [72]. Expression of the *ITGA10* gene, which encodes integrin-α, is associated with poorer outcomes, it was also found that TRIO and RICTOR proteins, involved in the signalling pathway for this integrin, can be inhibited by RAC inhibitor (activated by the two proteins) and an mTOR inhibitor; addition of these proteins inhibited the growth of tumour cells *in vitro* [78]. The most recent studies have been conducted on 41 MFS tumours. Exome sequencing and methylation studies were performed for all of them, and for some (29) also RNA sequencing [79] and then 140 selected genes for over 100 MFSs were examined. In total, 14 genes that control oncogenesis were detected, of which over 1/3 could potentially be a target for therapies. In MFS there are frequent changes associated with signalling by p53 and genes associated with cell cycle checkpoints (51 and 43% of cases, respectively). The authors also found three patterns of MFS methylation, associated with control mutations and clinical outcomes, and having an influence on patient survival. Unlike UPS, it seems that MFS is definitely a more homogeneous malignancy, and there are good perspectives for using targeted therapies here.

In the same study, RNA sequencing was also performed, and in 29 tested samples 1653 transcripts were detected, resulting from the fusion of two genes, including in one of them the *SCL37A-BRAF* fusion; in additional experiments it was demonstrated that it induced tumours in nude mice, so it is a controlling gene for a specific MFS [79]. The study also showed some correlations of changes in genes regulating the cell cycle, with worse survival outcomes. It was interesting to note that mutations in the *GNAS* gene seemed to protect against death caused by malignancy [79].

A large portion of MFS (14/30) overexpress MET [80] protein, and this is associated with the amplification of the *MET* gene and with polyploidisation of chromosome 7.

Another approach to the molecular analysis of sarcomas is to obtain cell cultures and conduct research on them. In general, unlike research related to DNA and RNA analysis, such work concerns only a few lines, and drawing conclusions from them is quite limited. On the other hand, it is possible to carry out studies on the effects of drugs, the ability of cells to invade, etc. One such study [81], carried out on cells from three patients, brought encouraging results for the *CD109* marker in identifying more aggressive MFS.

Osteosarcoma

Genes encoding tumour suppressors including p53, Rb, RECQL4 (ATP-Dependent DNA helicase Q4/RecQ Like helicase 4), BLM (Bloom Syndrome RecQ Like helicase/DNA helicase, RecQ-Like Type 2), and WRN (Werner Syndrome RecQ helicase Like/DNA helicase/RecQ-Like Type 3) proteins play a special role in the pathogenesis of osteosarcoma (OS). These proteins play a key role in the development of OS in patients with Li-Fraumeni syndrome, hereditary retinoblastoma, Rothmund-Thomson, Bloom and Werner syndrome [82]. There are currently no drugs that allow the restoration of the function of the mutant p53 protein, although many compounds have been tested in preclinical studies [83]. Although osteosarcomas do not have specific translocations, in contrast to, for example Ewing sarcoma, OS cells carry numerous loss of heterozygosity (LOH) lesions, reflecting the described variation in the number of gene copies in these tumours. While the OS have relatively few mutations in gene exons as compared to other solid tumours [84], the amount of amplification of genes in osteosarcoma is higher than for any other human malignancy. It is indicated that these are amplifications generated by chromothripsis for both paediatric and adult OS [85]. Circulating DNA released from OS cells including characteristic somatic mutations, such insertions, deletions, or translocations are detectable in the blood samples from OS patients. The mutations of the *TP53* gene are particularly useful for determination in a liquid biopsy [86]. Due to numerous chromosomal abnormalities and mutations, the OS appears to be a tumour potentially responding to immunotherapy, and current studies of immune checkpoint inhibitors use anti-PD-1 and anti-CTLA-4, including nivolumab ± ipilimumab (NCT02304458) and pembrolizumab (NCT02301039), as well as INF-α-2b (NCT00134030) and L-MTP-PE (liposomal muramyl tripeptide phosphatidylethanolamine) (NCT00631631; NCT02441309) [87].

In recent years, several groups have performed OS sequencing, including whole genome sequencing (WGS) from 47 OS samples with pairs of healthy control tissues, whole exome sequencing (WES) from 111 samples with a set of healthy control tissues, and whole-transcriptome sequencing from 36 samples [88–90]. Unfortunately, most of the studies published on OS concern *de facto* paediatric cases, and the lists of genes considered important for the development of childhood OS and OS in adults probably differ [82], although recently conducted selected genome studies indicate that they may be significantly analogous [85]. In studies of samples from paediatric tumours (mainly subtype osteoblastic and chondroblastic) it has been shown that the majority (> 70%) of tumours carry the mutated *TP53* or *RB* gene. Furthermore, analysis of the genome indicated further genes in which mutations contribute to the development of overall survival, including genes responsible for: 1) controlling the cell cycle and apoptosis (*p53*, *RB*1, *CDKN2A*, *CDK4*, *MDM2*, *MYC*, *CARD11*, *CTNND1*, *BLM*, *CCNE1*, *COPS3*, *PRKCA*); 2) PI3K-mTOR and

RAS signal pathways genes (*EGFR*, *GNAQ*, *GNAS*, *ALK*, *PDGFRA*, *PDGFRB*, *PIK3CA*, *AKT2*, *PIK3R1*, *PTEN*, *TSC2*, *VHL, CBL*); 3) Notch-signalling pathway genes (*NOTCH1-4*, *MAML2*, *FBXW7*, *PDPK1*, *AKT1*, *E1F4B*); 4) proteins of DNA damage repair (*BRCA*1, *BRCA2*, *MLH1*, *BAP1*, *ATM*, *WRN*); 5) chromatin modification proteins (*ATRX*, *FANCE*, *RECQL4*, *ARID1A*, *EP300*); 6) transcription regulation genes (*Runx1*, *GAS7*, *MLLT3*); and others [82]. In turn, genetic tests in adults and adolescents (< 16 years old) with OS showed that the genes regulating OS development in adults include *TP53*, *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), *AKT1* (AKT serine/threonine protein kinase 1), *H3F3A* (H3 histone family member 3A), *SETD2* (SET domain containing 2) and *FBXW7* (F-box and WD repeat domain containing 7, E3 ubiquitin protein ligase). This study also indicated that genes regulating angiogenesis (*TIE1* and *KD*R) can play an important role in OS development [84]. In addition, studies of adult tumours indicate IGF1 receptor (I*GF1R*) amplification in 14% of tumours [85]. In turn, research aimed at searching for diagnostic-prognostic biomarkers and analysing the level of gene expression in OS tumours led to the identification of characteristic profiles of protein expression and mRNA in OS cells. Deregulated levels of ErbB-2 (tyrosine kinase-type cell surface receptor HER2), cathepsin D, FBXW7 (F-box and WD repeat domain containing 7, the E3 ubiquitin protein ligase), microRNA miR-421, and HMGB1 (high-mobility group [non-histone chromosomal] protein 1) have been shown. It was also suggested that the expression of the Gla matrix protein may play a role in facilitating the spread of the tumour in metastatic lesions in the lungs [91]. A comparison of fresh biopsy material from the femoral and healthy femoral bone indicates that over 3300 genes are overexpressed and nearly 2000 have reduced expression in the OS. Among these genes, *BTNL9*, *MMP14*, *ABCA10*, *ACACB*, *COL11A1*, and *PKM2* have the highest difference in expression between tumour and normal bone. This study requires validation in a larger cohort of patients [92].

Currently, an interesting direction for research based on OS analysis is small RNA analysis, because it plays a regulatory role in relation to other genes. The characteristic small RNA deregulated in OS is miR-421. The expression level of miR-421 in serum is higher in OS patients than in healthy volunteers. In addition, miR-421 expression is higher in osteosarcoma tissues compared to adjacent normal tissues in 90% of OS patients. In addition, miR-421 expression levels in tissues from OS patients correlate with serum levels. Finally, patients with high miR-421 expression have a shorter overall survival than those with low expression, and miR-421 overexpression promotes proliferation, migration, and invasion of osteosarcoma cells. Other microRNAs of potential significance in the pathophysiology of OS include: miRNA-129-5p (miR-129-5p), miR-330-3p, miR-365, or miR-491-3p [93]. miR-21, -34a, -143, -148a, -195a, -199a-3p, and -382 regulate the activity of MAPK and PI3K/Akt signalling pathways in OS [94]. Determining the diagnostic and prognostic significance of small RNA in OS requires meta-analysis and validation in prospective studies. This is important as small RNAs are easily detectable in the blood of patients and can potentially be used to develop diagnostic tests [95].

Functional research in the field of basic sciences describes the number of mutations and their order necessary/minimal for OS development. An inductor gene that can cause bone malignancy is classified as primary. The group of primary OS inducers includes the following genes: *TP53, NOTCH1, MYC, FOS, NF2, WIF1, BRCA2, APC, PTCH1*, and *PRKAR1A*. However, the penetration of each of the above genes are different. Damage to *TP53* and *NOTCH* genes can induce tumour formation with close to 100% penetration, while mutations at *WIF1* and *BRCA2* can induce OS development in only a small percentage of patients. A gene which perturbation cannot independently initiate a malignant process in the bone is classified as a synergistic gene. A deregulated synergistic gene can accelerate tumour initiation and growth, but it can also affect disease progression through germline mutation before the primary gene is damaged by somatic mutation. The group of synergistic genes in OS includes *RB1*, *TWIST*, *PTEN*, and *JUN* [82].

The meta-analysis of available proteomic data comparing protein expression between OS cells and healthy osteoblasts revealed a list of proteins that are potential targets of drugs currently available on the market. Although this is a preliminary analysis, the authors suggest that *in vitro* and *in vivo* studies should be carried out to evaluate the potential benefit of use of the indicated substance against OS. Proteins indicated as potential drug targets in OS include DNMT1 (DNA [cytosine-5]-methyltransferase 1) — target for azacytidine (Vidaza) and decitabine (Dacogen); ERBB2 (receptor tyrosine-protein kinase erbB-2) — a target for trastuzumab (Herceptin) and lapatinib (Tycerb) afatinib (GIOTRIF/ /GILOTRIF), pertuzumab (PERJETA); GSR (mitochondrial glutathione reductase) — target for carmustine (GLIADEL® WAFER); HDAC1 (histone deacetylase 1) — target for vorinostat (Zolinza); HDAC2 (Histone deacetylase 2) — target for romidepsin (Istodax); KIT (mast/stem cell growth factor receptor kit) — target for imatinib (Gleevec), sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), dasatinib (Sprycel), axitinib (Inlyta) and nilotinib (Tasigna); FGFR1 (Fibroblast growth factor receptor 1) — target for lenvatinib (Lenvima); MET (Hepatocyte growth factor receptor)

— target for cabozantinib (COMETRIQ), crizotinib (XALKORI); MTOR (serine/threonine protein kinase mTOR) — target for temsirolimus (Torisel), everolimus (Afinitor); PARP1 (poly [ADP-ribose] polymerase 1) — target for olaparib (AZD2281); PDGFR α (platelet-derived growth factor receptor alpha) — target for imatinib (Gleevac), sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), nilotinib (Tasigna), axitinib (Inlyta), and dasatinib (Sprycel) and *PSMC2* (26S protease regulators subunit 7) — targets for bortezomib (Velcade) [96]. The list of the above potential targets for drugs also includes those regulated by drugs currently evaluated in phase I/II clinical trials in OS, including bevacizumab (NCT00667342), sorafenib (NCT00889057, NCT01804374, regorafenib (NCI02048371), pazopanib (NCT01956669; NCT01759303), cabozantinib (NCT02243605), sirolimus (NCT02517918), everolimus (RAD001) (NCT01804374), and glembatumumab vedotin (NCT02487979) [87]. An interesting potential target for treatment in OS is also GD2 disialoganglioside. It has been shown that anti-GD2 therapy — chimeric anti-GD2 antibody dinutuximab — improves survival outcomes in patients with neuroblastoma, and almost all OS cases express a large amount of GD2. Currently, studies are being conducted with several anti-GD2 molecules, including dinutuximab (NCT02484443), Hu3F8 (NCT02502786), and Hu14.18K322A (NCT00743496), and cell therapy with anti-GD2 lymphocytes (NCT02173093, NCT02107963) [87].

Chondrosarcoma

Although the biology of chondrosarcoma (CHS) is still unclear, it is known that there is an increased number of genetic aberrations together with dedifferentiation of CHS from low to high grade. The role of p53 in the pathology in CHS remains unexplained, but the presence of p53 protein overexpression, 17p1 chromosomal aberration, and *TP53* mutations present in almost all poorly differentiated CHS suggests that *TP53* mutation/mutations are a late event associated with CHS progression. This is also confirmed by 12q13 (MDM2) amplification and loss of 9p21 (*CDKN21/p16/INK4A* and *INK4A-p14ARF*) [97]. At the same time, irregularities of c-*MYC* appear to occur in the early stages of tumorigenesis in all chondrosarcomas, and overexpression of metalloproteinases MMP-2, MMP-MT1, and TIMP2 and abnormal methylation of p16 and E-cadherin present in anaplastic cells of dedifferentiated CHS [98]. In addition, in 69% of patients with conventional CHS and 44% with dedifferentiated CHS, a high phosphorylation of S6 kinase, a surrogate of the PI3K-mTOR pathway activity, was detected [99]. BEZ235 — an inhibitor of PI3K and mTOR — significantly inhibited division of CHS cell lines and CHS tumour growth in an animal model, suggesting that the inhibition of PI3K/mTOR is a potentially new therapeutic strategy, which could be evaluated in the early phases and could be possible also in patients after failure of previous treatment with kinase inhibitors (pazopanib) [100, 101].

Recent studies have shown frequent occurrence of mutations in *IDH1* (isocitrate dehydrogenase 1) or *IDH2* genes in almost half of chondrosarcomas, including the prognostic significance of these mutations [102]. IDH proteins encoded by the *IDH* genes catalyse oxidative decarboxylation of isocitrate, producing αKG and CO_2 in the citric acid cycle (CAC), also called the Krebs cycle. It is known that these mutations result in the production of D-2 hydroxyglutarate (2HG) from αKG conversion (alpha-ketoglutarate). 2HG accumulates in the cells and inhibits the activity of αKG-dependent enzymes, leading to hypermethylation of DNA and histones, which results in a change in the expression of genes associated with oncogenesis. 2HG inhibits TET2 (TET methylcytosine dioxygenase 2) the activity of a DNA-modifying enzyme dependent on αKG, responsible for DNA demethylation. Thus, 2HG causes hypermethylation of DNA (by inhibition of demethylation). 2HG also inhibits αKG-dependent histone demethylase of JHKDM (JmjC-domain containing histone lysine a demethylases). JHKDM modifies chromatin and thereby regulates gene expression. The IDH2 mutation has been shown to induce 2HG-dependent DNA hypermethylation in chondrosarcoma cells, which inhibits mesenchymal differentiation. Treatment with a 5-azacitidine, a demethylating compound, can potentially reverse this block of differentiation. There are ongoing clinical trials evaluating the clinical activity of novel IDH inhibitors. AG-221 — an oral IDH2 inhibitor — is currently being tested in phase I/II studies in patients with chondrosarcoma with the *IDH2* mutation (NCT02273739). Inhibitors IDH AG-881 and AG-120 are also being evaluated in phase I studies in chondrosarcoma with *IDH1* and/or *IDH2* mutation (NCT02481154/NCT02073994); combination of metformin with chloroquine in CHS patients with *IDH1/2* mutations is also undergoing clinical trials (NCT02496741) [99].

Proteomic analysis of the entire chondrosarcoma kinome revealed that the AKT1/GSK3B pathway was clearly active in the case of CHS. In addition, the PDGFR pathway and the Src kinase family were active; however, this activation did not translate into effectiveness of inhibiting the proliferation of CHS cells by imatinib or dasatinib except an *in vitro* model, and the objective response rates in the phase II studies were low [103, 104]. In CHS, the hypermutability of the main cartilage collagen gene *COL2A1* was identified, including insertions, deletions, and rearrangements in 37% of cases. The described mutations may interfere with

normal collagen biosynthesis. In addition, mutations were identified in *IDH1* or *IDH2* (59% of cases), and *TP53* (20%) genes, RB1 pathway (33%), and Hedgehog pathway (18%) [105].

The IHH (Indian Hedgehog) pathway and the parathyroid hormone-related peptide (PTHrP) pathway play a key role in the differentiation of healthy chondrocytes, and it has been proven that constitutive IHH signalling plays a key role in the pathogenesis of chondrosarcomas. Abnormal activation of this pathway leads to continuous signals from IHH that induce chondrocyte proliferation and the secretion of PTHrP from chondrocytes into the extracellular matrix. By auto- and paracrine signalling, PTHrP mediates the inhibition of chondrocyte differentiation and apoptosis, thus maintaining cells in the state of cell division [99]. While preclinical data on the activity of IPI-926 (saridegib — oral Hedgehog pathway inhibitor) indicated good activity of this compound, clinical data from a phase II study in patients with advanced chondrosarcoma were not satisfactory [106, 107]. Similarly, vismodegib (GDC-0449) treatment assessed in a phase II study did not bring the expected results; the median progression-free survival (mPFS) was only 3.5 months, and the median overall survival (mOS) was 12.4 months [108]. These disappointing clinical outcomes may indicate a ligand-independent activation of the Hh pathway in CHS, which may occur in the case of loss of PTCH function mutation or SMO mutation, causing loss of function and activation of the downstream pathway [99].

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