
# Etiology and Predisposition

# 3

As it occurs for most human neoplasms, the etiology of most soft tissue tumors is basically unknown, and the vast majority of them are sporadic. In a minority of cases, the following risk factors have been identified:

(a) Among **physical agents**, ionizing radiations are a well-known risk factor. For instance, radiotherapy increases by 10–50 times the risk of some soft tissue sarcomas (e.g., angiosarcoma and undifferentiated pleomorphic sarcoma) as well as the risk of osteosarcoma; of note, the interval between radiation exposure and tumor development is averagely 10–15 years; noteworthy, the combination with chemotherapy appears to shorten the time to radiation-induced sarcoma.
(b) Some **chemical agents** (e.g., herbicides such as phenoxyacetic acid, wood preservatives containing chlorophenol, contrast medium thorotrast/thorium oxide, industrial chemicals such as vinyl chloride and arsenic) are also recognized carcinogens associated with increased risk of soft tissue sarcomas (with special regard to angiosarcoma).
(c) **Biological agents** (i.e., viruses) have been linked to the development of specific soft tissue sarcomas: the best example is the tight relationship between human herpesvirus 8 (HHV8) and Kaposi sarcoma.
(d) **Chronic lymphedema** (following lymphadenectomy but also filarial infection and congenital primary lymphedema) is associated with an increased risk of lymphangiosarcoma, a condition known as Stewart-Treves syndrome.
(e) In a minority of cases, soft tissue tumors run in families where they contribute to the phenotype of **cancer predisposition syndromes**, such as hereditary retinoblastoma (associated with the development of different types of sarcomas), Li-Fraumeni syndrome (multiple types of sarcomas), Werner syndrome (undifferentiated pleomorphic sarcoma as well as other sarcomas), Gardner syndrome (desmoid tumor), Carney-Stratakis syndrome (GIST and paraganglioma), Gorlin syndrome (rhabdomyosarcoma), tuberous sclerosis (PEComas), and so on. These hereditary syndromes are generally due to germline high penetrance



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inactivation of tumor suppressor genes (e.g., RB1 in hereditary retinoblastoma, TP53 in Li-Fraumeni syndrome, NF1 in neurofibromatosis, and so on) or activation of oncogenes (e.g., KIT in familial GIST). The details of these as well as many other conditions predisposing to soft tissue tumor development are described in the sections dedicated to single tumors (in the second part of this book).

Due to their rarity, sarcomas have not been the target of large epidemiological studies. A recently launched multicentric population-based case-control French study (ETIOSARC) will investigate the role of lifestyle and environmental and occupational factors in the occurrence of sarcomas among adults.

As regards the molecular etiopathogenesis of **sporadic soft tissue tumors**, both germline and somatic genetic alterations have been described. Low penetrance germline polymorphisms (mainly single nucleotide polymorphisms, SNP) of genes such as TP53, ATM, ATR, BRCA2, and ERCC2 have been associated with an increased risk of tumor development, but the epidemiological rarity of these neoplasms coupled with their clinicopathological heterogeneity has so far hindered the conduction of genome-wide studies on large series of patients affected with specific tumor types, which prevents from defining the host genetic background conducive to sporadic sarcoma development.

From the viewpoint of somatic genetic alterations, soft tissue tumors (including benign and malignant neoplasms) can be divided into two main categories (each including approximately 50% of soft tissue sarcomas):

(a) Neoplasms with specific recurrent (and sometimes pathognomonic) genetic alterations such as chromosomal translocations leading to the formation of fusion genes (also known as chimeric genes and gene fusions), mutations (e.g., activating mutations of KIT oncogene in GIST), and gene amplifications (e.g., MDM2 amplification in well-differentiated and dedifferentiated liposarcoma). These tumors are also characterized by simple karyotypes, with some exceptions (e.g., dedifferentiated liposarcoma). As regards fusion genes, more than 150 such gene fusions have been so far described in approximately one third of soft tissue tumors and 20% of soft tissue sarcomas (a dedicated database of chromosome aberrations and gene fusions in human cancers is available at *https://mitelmandatabase.isb-cgc.org/*). In most cases, these chimeric genes generate transcription factors such as (e.g., EWSR1-ATF1 in clear cell sarcoma; EWSR1-FLI1 in primitive neuroectodermal tumor/Ewing sarcoma family); other fusion genes encode receptor tyrosine kinases (e.g., ETV6-NTRK3 in congenital mesoblastic nephroma; ALK-containing fusion genes in inflammatory myofibroblastic tumor), growth factors (e.g., COL1A1-PDGFB in dermatofibrosarcoma protuberans; COL6A3-CSF1 in tenosynovial giant cell tumor), chromatin regulators (e.g., BCOR-CCNB3 in undifferentiated round cell sarcoma and SS18-SSX in synovial sarcoma), or other proteins known to be involved in carcinogenesis (e.g., MIR143-NOTCH in glomus tumors). Of note, some fusion genes are present in most (if not all) cases of a given tumor type (e.g., NAB2-STAT6 in solitary fibrous tumor; EWSR1-WT1 in desmoplastic small round cell tumor), but others can be found only in a subset of cases (e.g.,

about 50% of inflammatory myofibroblastic tumors harbor ALK-containing fusion genes), and others can have more than just one gene partner (e.g., SS18-SSX1 and SS18-SSX2 in synovial sarcoma; FUS-DDIT3 and EWSR1-DDIT3 in myxoid liposarcoma); furthermore, in the same soft tissue tumor, different types of fusion genes can be detected, the same fusion gene can be identified in different soft tissue tumors, and some fusion genes are shared with non-soft tissue neoplasms (e.g., NTRK-containing fusion genes).

(b) Neoplasms with complex karyotypes but no specific genetic pattern (e.g., undifferentiated pleomorphic sarcoma, pleomorphic liposarcoma, leiomyosarcoma, pleomorphic rhabdomyosarcoma, and malignant peripheral nerve sheath tumor). The mutational landscape of these tumors shows that—unlike carcinomas—they are characterized mainly by copy number alterations with low mutational burden (associated with a low incidence of microsatellite instability, MSI) and only a few genes recurrently mutated across different histological types (e.g., TP53, ATRX, RB1, NF1, PIK3CA, and PTEN). For a list of most mutated genes in selected soft tissue tumors, → see Table 3.1.

**Table 3.1** Top mutated genes in selected soft tissue tumors (only neoplasms with at least 100 samples available were selected). (Source: Catalogue Of Somatic Mutations In Cancer (COSMIC, *https://cancer.sanger.ac.uk/cosmic*))

| Tumor | Gene | Mutated (%) |
|---|---|---|
| Angiosarcoma | TP53 | 27 |
| | KRAS | 18 |
| | PLCG1 | 11 |
| | KDR | 8 |
| | CIC | 4 |
| | NRAS | 3 |
| | PIK3CA | 3 |
| Liposarcoma NOS | PIK3CA | 9 |
| | TP53 | 8 |
| | EP300 | 7 |
| | KMT2D | 4 |
| | ATRX | 4 |
| | CIC | 3 |
| | CTNNB1 | 2 |
| | NF1 | 2 |
| | PTEN | 2 |
| | HRAS | 2 |
| | RB1 | 2 |
| | KDM6A | 2 |
| | PBRM1 | 2 |
| | KIT | 1 |
| | EGFR | 1 |
| | FBXW7 | 1 |
| | ERBB2 | 1 |
| | APC | 1 |

(continued)

**Table 3.1** (continued)

| Tumor | Gene | Mutated (%) |
|---|---|---|
| Desmoid tumor | CTNNB1 | 72 |
| | APC | 18 |
| MPNST | NF1 | 21 |
| | TP53 | 12 |
| | BRAF | 2 |
| | CDKN2A | 2 |
| | KRAS | 1 |
| Neurofibroma | NF1 | 40 |
| Schwannoma | NF2 | 43 |
| | SMARCB1 | 4 |
| Leiomyoma | MED12 | 51 |
| | TP53 | 4 |
| Leiomyosarcoma | TP53 | 33 |
| | ATRX | 23 |
| | RB1 | 16 |
| | MED12 | 8 |
| | PTEN | 5 |
| | CARD11 | 5 |
| | KRAS | 4 |
| | ASXL1 | 4 |
| | NSD1 | 4 |
| | TOP1 | 4 |
| | KMT2A | 4 |
| | ATM | 3 |
| | ARID1A | 3 |
| | ARID2 | 3 |
| | BRCA2 | 3 |
| | AR | 3 |
| | PIK3CA | 2 |
| | CDH1 | 2 |
| | NF1 | 2 |
| | BRAF | 2 |
| | ATM | 2 |
| Rhabdoid tumor | SMARCB1 | 23 |
| Rhabdomyosarcoma (embryonal) | TP53 | 16 |
| | NRAS | 15 |
| | MYOD1 | 11 |
| | NF1 | 8 |
| | DICER1 | 7 |
| | HRAS | 6 |
| | PIK3CA | 5 |
| | PTPN11 | 3 |
| | ALK | 3 |
| | CTNNB1 | 3 |
| | ERBB2 | 3 |
| | NOTCH1 | 2 |

Advances in the knowledge of the molecular aberrations underlying the pathogenesis of soft tissue tumors is having a major impact on the diagnostic, prognostic, and therapeutic approach to these tumors: for this reason, the most relevant genetic features are reported in the paragraph entitled "Biomarkers" within the sections dedicated to each soft tissue tumor, in the second part of the book.

## Suggested Readings

Ballinger (2016) Monogenic and polygenic determinants of sarcoma risk: an international genetic study. Lancet Oncol 17(9):1261–1271

Barretina (2010) Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat Genet 42(8):715–721

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Cancer Genome Atlas Research Network (2017) Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. Cell 171(4):950–965

Farid (2016) Sarcomas associated with genetic cancer predisposition syndromes: a review. Oncologist 21(8):1002–1013

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Lacourt (2019) ETIOSARC study: environmental aetiology of sarcomas from a French prospective multicentric population-based case-control study-study protocol. BMJ Open 9(6):e030013

Mariño-Enríquez (2016) Molecular pathogenesis and diagnostic, prognostic and predictive molecular markers in sarcoma. Surg Pathol Clin 9(3):457–473

Mertens (2016) Gene fusions in soft tissue tumors: recurrent and overlapping pathogenetic themes. Genes Chromosomes Cancer 55(4):291–310

Schaefer (2018) Contemporary sarcoma diagnosis, genetics, and genomics. J Clin Oncol 36(2):101–110

Suurmeijer (2019) New advances in the molecular classification of pediatric mesenchymal tumors. Genes Chromosomes Cancer 58(2):100–110

Thway (2020) Update on selected advances in the immunohistochemical and molecular genetic analysis of soft tissue tumors. Virchows Arch 476(1):3–15

Zhang (2017) Chemotherapy with radiotherapy influences time-to-development of radiation-induced sarcomas: a multicenter study. Br J Cancer 117(3):326–331