Current Oncology Reports (2020) 22: 124
https://doi.org/10.1007/s11912-020-00985-w

Synovial Sarcoma: A Complex Disease with Multifaceted Signaling and Epigenetic Landscapes

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Accepted: 7 September 2020 / Published online: 6 October 2020
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ABSTRACT

Purpose of Review Aside from a characteristic *SS18–SSX* translocation identified in almost all cases, no genetic anomalies have been reliably isolated yet to drive the pathogenesis of synovial sarcoma. In the following review, we explore the structural units of wild-type SS18 and SSX, particularly as they relate to the transcriptional alterations and cellular pathway changes imposed by SS18–SSX.

Recent Findings Native SS18 and SSX contribute recognizable domains to the SS18–SSX chimeric proteins, which inflict transcriptional and epigenetic changes through selective protein interactions involving the SWI/SNF and Polycomb chromatin remodeling complexes. Multiple oncogenic and developmental pathways become altered, collectively reprogramming the cellular origin of synovial sarcoma and promoting its malignant transformation.

Summary Synovial sarcoma is characterized by complex epigenetic and signaling landscapes. Identifying the operational pathways and concomitant genetic changes induced by *SS18–SSX* fusions could help develop tailored therapeutic strategies to ultimately improve disease control and patient survivorship.

Keywords Synovial sarcoma · neoplastic pathways · SS18–SSX · SWI/SNF complex · Polycomb complex · chromatin modulation

Introduction

Synovial sarcoma is a rare soft-tissue malignancy that grows predominantly in the lower limbs of young adults [1, 2]. In spite of its name, it does not stem from the synovium and cumulative evidence points towards a mesenchymal origin for the disease [3–8]. The tumor harbors a stable karyotype with few secondary cytogenetic alterations [9, 10, 11•, 12••]. It is driven by a unique genetic exchange that fuses the *SS18* gene with an *SSX* partner [13, 14]. The ensuing *SS18–SSX* translocation is the only recurring genetic event reliably isolated in almost all cases and encodes chimeric proteins that modulate transcriptional and epigenetic pathways through precise protein interactions [13, 15–20].

Current therapeutic protocols for synovial sarcoma are guided by the disease's location and stage. Wide resection with negative surgical margins is the mainstay of therapy for primary disease, may suffice for small (< 5 cm) localized tumors, but is insufficient for more advanced ones [21, 22]. Radiation as a surgical adjuvant can be beneficial for local control of larger tumors. While systemic chemotherapy has been employed for large, high grade tumors, it has limited therapeutic benefit in patients with metastatic disease who still exhibit a dismal prognosis [23]. The dearth of effective therapeutic strategies in synovial sarcoma imposes a need to

This article is part of the Topical Collection on *Sarcomas*

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identify functional oncogenic networks as means to discover new biologic targets and potential therapeutic avenues.

The following review examines the structural units of wild-type SS18 and SSX, and discusses the transcriptional alterations imposed by the SS18–SSX fusion proteins. It uncovers operational neoplastic events and pathways in synovial sarcoma and highlights treatment modalities that could ultimately help improve disease control and patient survivorship.

Functional Domains of SS18 and SSX

SS18 maps to the long arm of chromosome 18 and encodes a conserved protein with ubiquitous expression [20, 24, 25]. It contains three moieties, none of which is capable of direct DNA binding [14, 15, 17–19, 26–28] (Fig. 1). The SNH domain is located on the amino-terminal tail of SS18 and mediates some of its transcriptional regulation. The NLS sequence contains the protein's nuclear translocation signal, whereas the carboxy-terminal QPGY motif has transactivating properties. The latter is rich in glutamine, proline, glycine, and tyrosine residues, mirroring sequences of integral subunits of the SWI/SNF chromatin-remodeling complex [18, 29–31]. SS18 carries one SH3 and three SH2 modules directly implicated in transduction signaling pathways [32–34].

The *SSX* family comprises nine fully delineated homologous genes (*SSX1* through *SSX9*), contiguously confined to the short arm of chromosome X [35, 36]. Owing to their restricted expression to the normal testis and some neoplastic diseases, the translated SSX peptides are classified as cancer-testis antigens [35–37]. Sequence alignment and structural region analyses outlined two shared regions among these proteins [14, 18, 26, 35, 38, 39] (Fig. 1). They include an amino-terminal KRAB and a carboxy-terminal SSXRD domains, both involved in transcriptional repression. Aside from its potent repressive properties, SSXRD facilitates the proteins' nuclear localization. SSX peptides display minor discrepancies within a sequence in close vicinity of SSXRD, designated SSXDD.

Functional Domains Retained in SS18–SSX

Among all *SSX* genes, only *SSX1*, *SSX2*, and *SSX4* have hitherto been fused to *SS18* in synovial sarcoma [40–43]. The reason behind this selectivity remains a subject of constant controversy but may involve privileged gene orientation and/or accessibility. *SS18* or *SSX* overexpression alone does not generate tumors, implicating both partners of *SS18–SSX* in synovial sarcomagenesis [20, 44]. Investigating the domains retained in the final oncogenic fusions and their non-transforming counterparts is paramount for a better understanding of the pathogenesis of the disease and the development of potential therapeutic avenues.

SS18–SSX chimeras are generated by the substitution of SS18 carboxy-terminal residues with an SSX carboxy-

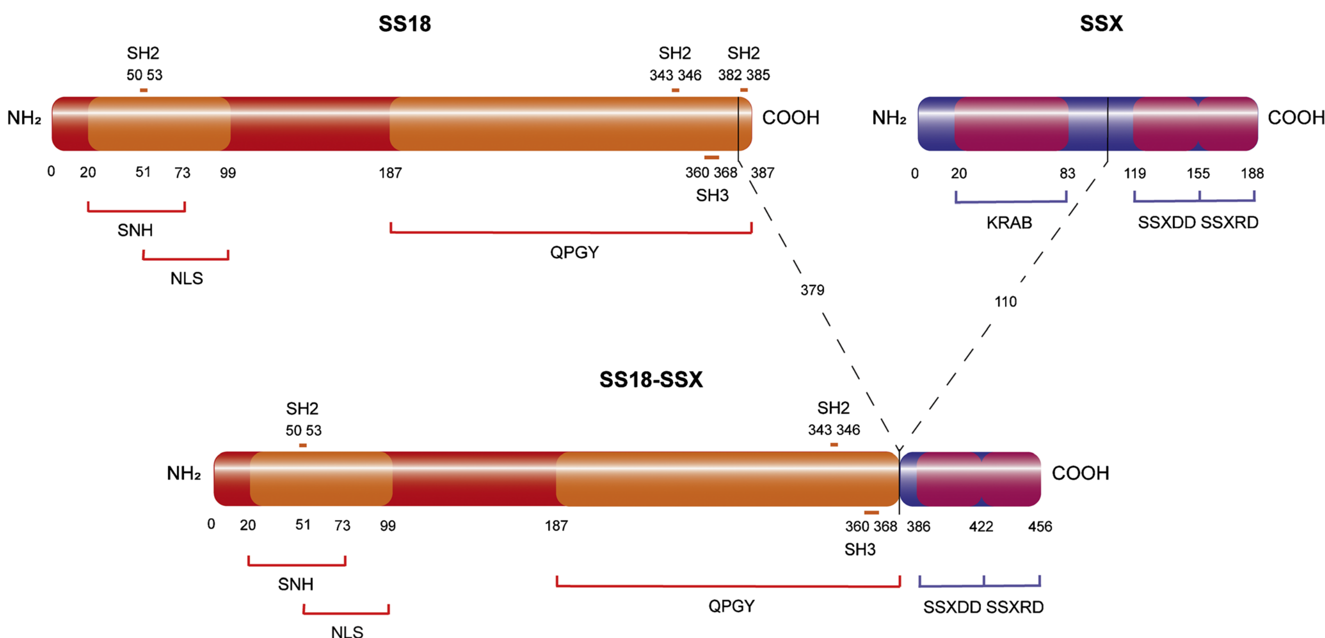

Fig. 1 Functional domains of SS18, SSX, and SS18-SSX. Wild-type SS18 is 387 amino acids long and contains an SNH domain (amino acids 20 to 53), an NLS motif (amino acids 51 to 99), and a QPGY sequence (amino acids 187 to 387). Wild-type SSX is a 188 amino acid protein that includes a KRAB domain (amino acids 20 to 83), an SSXDD sequence (amino acids 119 to 154), and an SSXRD motif (amino acids 155 to 188). The SS18-SSX oncoprotein encompasses 456 amino acids and preserves the amino-terminal 379 amino acids of SS18 as well as the carboxy-terminal 111 amino acids of SSX. The generated translocation retains the entire SNH, NLS, SSXDD, and SSXRD domains of the wild-type peptides, as well as most of the QPGY motif

terminal tail (Fig. 1). Their secondary and tertiary protein structures do not entirely recapitulate the domains predicted by their wild-type components [14, 28, 45–50]. SNH, NLS, and SSXDD are invariably retained, as well as most of the SS18 QPGY activation motif. Although seldomly reported, truncated fusion variants lacking SSXRD argue against a major role for this module in synovial sarcomagenesis [44, 51]. Most divergences between transforming (*SS18–SSX1*, *SS18–SSX2*, and *SS18–SSX4*) and laboratory-constructed non-oncogenic fusions (*SS18–SSX3* and *SS18–SSX5*) are mapped to a region composed of two amino acids within their SSXDD domain [20]. The involvement of SH2, SH3, and KRAB domains in the final protein hybrids is inconsistent, and their contribution to the development of synovial sarcoma remains inconclusive.

Regulatory Mechanisms Mobilized by SS18–SSX

Contrasting with conventional translocations, SS18–SSX peptides do not generate specific transcription factors but rather combine chromatin modifiers with novel properties [19, 52]. They are preferentially sequestered in nuclear bodies, where they interact with histones and core regulatory proteins [15, 17, 20, 26, 53–55] (Fig. 2).

SS18–SSX hybrids associate with constitutional members of the SWI/SNF chromatin-remodeling complex, including SMARCA2, SMARCA4, and SMARCA5 [17, 19, 44, 56]. Cells carrying *SS18–SSX* demonstrate significant variations in *SMARC* genes expression, including *SMARCB1*, a tumor suppressor [19, 57, 58]. Specific to synovial sarcoma is the competition between SS18 and SS18–SSX for assembly within SWI/SNF, expelling SMARCB1 for degradation, and leading to a biochemically aberrant complex that disrupts gene expression [12, 20].

SS18–SSX oncoproteins also aggregate with core subunits of the Polycomb repressive complexes (BMI1 and RING1A within PRC1, as well as SUZ12, EZH2, and EED within PRC2), and the histone deacetylase HDAC1 [16, 18, 19, 26, 59–61]. They partially regulate transcription through BMI1 depletion and protein recruitment to specific DNA regions enriched with H3K27me3, a PRC2-related epigenetic marker that correlates with Polycomb gene silencing [20, 59, 60, 62–67]. Genetic repression may also relate to the activity of *EZH2*, the transcription of which is enhanced by SMARCB1 depletion, explaining the overlap between downregulated genes in synovial sarcoma cell lines with the ones repressed by the PRC2 components [68–70]. Upregulated genes in this disease, however, display an increased H3K4me3 epigenetic signal in their promoters, which antagonizes H3K27me3 and promotes transcriptional activation [12••, 19].

SS18–SSX indirectly regulates several proteins with histone acetylase/deacetylase activity. SIN3A, a transcriptional repressor that associates with SMARCA2, SMARCA4, and HDAC1/2, activates its downstream effectors by binding SS18–SSX peptides [71–74]. The latter serve as scaffold proteins that combine the transcription activator ATF2 with the

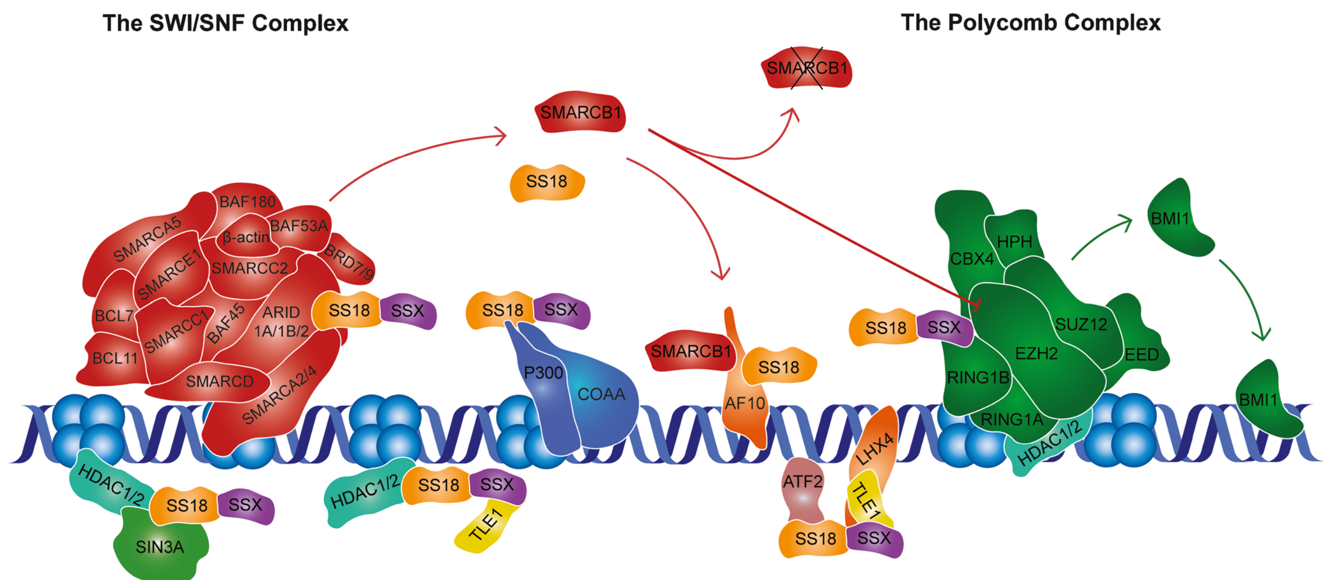

Fig. 2 Mechanisms of synovial sarcomagenesis. Blunted arrows (⊥) indicate inhibition, whereas pointed arrows (➔) imply induction. The generated SS18-SSX oncoprotein competes with wild-type SS18 for assembly within the SWI/SNF activator complex, ejecting the tumor suppressor SMARCB1 for degradation. The latter can also inhibit the Polycomb repressor complex (through EZH2 depletion) and associate with both the wild-type SS18 and the transcription factor AF10 to modulate gene expression. The fused peptide can also remodel chromatin and alter gene transcription through its interaction with co-effectors (SIN3A, TLE1, and P300), transcription factors (ATF2 and LHX4), and histone deacetylases (HDAC1/2)

corepressor TLE1, generating a multimeric silencing complex that inhibits ATF2 target promoters via TLE1-mediated HDAC1 recruitment and H3K27me3 labeling [56, 59]. These constructs bind and mitigate the activating properties of COAA, a cofactor that interacts with the P300 histone acetyltransferase and participates in post-transcriptional RNA splicing [75–78]. They modulate several microRNAs overexpressed in synovial sarcoma compared with other soft-tissue malignancies [79–82]. HDAC2 protects SS18–SSX oncopeptides degradation, allowing them to tether P300 and inhibit fibronectin matrix adhesion while increasing cellular motility and invasiveness [32, 83, 84]. SS18–SSX may also associate with transcription factors, such as AF10 and LHX4, to promote the development of synovial sarcoma [27, 39]. Of those, AF10 requires SMARCB1 to interact with other proteins and regulate transcription [85].

Models of Synovial Sarcomagenesis

Evidence pertaining to the potential mechanisms exploited by SS18–SSX constructs to reprogram the cell of origin of synovial sarcoma and promote malignant transformation is still preliminary (Fig. 2). A dynamic equilibrium between both SWI/SNF- and Polycomb-mediated epigenetic alterations as well as H3K27me3 and H3K4me3 signaling marks at native and de novo gene targets seems to be important for tumor formation. SS18–SSX peptides possess RNA splicing and modulatory properties and may interact with yet unidentified transcription factors and coeffectors [75, 76]. Because of the different mechanisms affected by these oncoproteins, multiple cellular functions and signaling networks are markedly disrupted in synovial sarcoma.

Neoplastic Events

Cell-Cycle Disruption

Synovial sarcoma is characterized by an aberrant cell-cycle activity. Cyclin (*CCN*) and cyclin-dependent kinase (*CDK*) genes are upregulated in the disease, whereas cyclin-dependent kinase inhibitors (*CDKNs*) are repressed, resulting in an overall enhanced cellular proliferation [8, 19, 57, 58, 70, 86]. To date, only one *CCND1* pathologic mutation has been reported in synovial sarcoma [10]. SS18–SSX peptides prevent cyclin D1 proteasomal degradation in serum-starved monolayer cultures and repress *CDKN2A* transcription [56, 87, 88]. Nuclear immunoreactivity for cyclins A, D1, and E is noted in synovial sarcoma but is not associated with patient survivorship [86, 89–94].

Apoptosis Escape

Apoptosis evasion allows synovial sarcoma cells to survive and proliferate, despite the upregulation of both pro- and anti-apoptotic genes [41, 58, 60, 70, 86, 95]. In murine embryonic fibroblasts transfected with *SS18–SSX*, *Bcl2* is increased, whereas *Mcl1* and *Bcl2a1* expression is significantly repressed through mechanisms involving the ATF2/TLE1 inhibitory complex [95]. Synovial sarcoma specimens stain positive for most apoptotic inducers and inhibitors, of which BCL2 is detected in virtually all cases [41, 86, 96–102]. *Bcl2* induction in *SS18–SSX*-positive Myf5 myoblasts accelerates synovial sarcomagenesis, but its inhibition, combined with doxorubicin, results in minimal synergistic effect on transformed cells and generated tumors [95, 103, 104]. Conversely, specific BCL2L1 repression hampers in vitro and in vivo tumoral growth [104]. Although BCL2 and BAX levels do not specifically predict survival in synovial sarcoma patients, multivariate analyses identified apoptosis as an independent indicator of worse prognosis [97, 101]. This might be explained by the complexity of apoptosis, as well as its tight association with cell proliferation, propelling synovial sarcoma cells into a more aggressive pro-survival state.

Cell Contact Inhibition

Synovial sarcoma cells circumvent contact inhibition, and genes involved in the cadherin–catenin adhesion system are upregulated in the disease [57, 105–107]. Sequencing and single-strand conformation polymorphism analyses revealed some tumor specimens to harbor mutations of undetermined significance in *CDH1* and *CTNNB1*, respectively encoding E-cadherin and β-catenin, contrary to most synovial sarcoma cell lines devoid of any activating aberrations within these genes [9, 94, 108–113]. Albeit displaying a peripheral immunoreactivity, the expression of cadherins and catenins (α, β, and γ) is reduced in the disease [92, 99, 105, 108, 111, 114, 115]. Their nuclear relocation may, at least partially, explain the scarcity of intercellular junctions on synovial sarcoma cell periphery, an event that promotes the tumor's invasion and correlates with worse patient survivorship [108].

Chemotaxis Modulation

The functional significance of chemotaxis in synovial sarcoma is yet to be fully explored. Human specimens and *SS18–SSX*-positive cells variably express several genes involved in chemotaxis regulation, *CXCL12* and *CXCR4* in particular [8, 19, 57, 58, 61, 107, 116]. Transcripts of the latter have been less frequently detected in monolayer tumoral cells than in spheroid cultures, possibly leading to cellular acquisition of anchorage-independent growth properties [116, 117].

Oncogenic Pathways

Receptor Tyrosine Kinase Pathways

Ephrin Pathway

Albeit preliminary, recent reports imply a role for the ephrin (Eph) pathway in synovial sarcoma migration. Gene microarray and phosphoproteomic analyses revealed an abundant upregulation of genes encoding ephrin ligands and receptors in the disease [57, 58, 106, 107, 118, 119]. A significant deregulation of several genetic components of the Eph signaling pathway is documented in cells carrying *SS18–SSX* transcripts [8, 19, 60, 61, 84, 120]. Such cells are positive for ephrin B1 and several receptors, of which, only EphA2 and EphB2 are phosphorylated [84, 119]. NIH3T3 murine fibroblasts dissociate and retract their neurite processes upon *SS18–SSX* expression, a repulsion phenotype that was promoted by EphB2 stimulation [84]. Clinically, both EphB2 and EphB4 are detected in synovial sarcoma specimens [84, 107].

Epidermal Growth Factor Pathway

Despite being dysregulated in synovial sarcoma, the epidermal growth factor (EGF) pathway does not seem to be relevant for the disease's pathogenesis. A single investigation of 17 patients with synovial sarcoma isolated *TGFA* mRNAs in all tumors analyzed [92]. Mutations and amplifications of *ERBB1* (*EGFR*, *HER1*), *ERBB2* (*HER2*), and *ERBB3* (*HER3*) failed to correlate with their corresponding proteins' expression in the disease [57, 58, 92, 98, 107, 121–125]. Sequencing analyses revealed sporadic missense mutations of *ERBB1* and *ERBB4* in synovial sarcoma [10, 126, 127]. Encoded ERBB peptides are identified in *SS18–SSX*-positive cell lines and lysates, as well as synovial sarcoma specimens [92, 98, 100, 119, 121, 124–132]. In this disease, ERBB1 or ERBB2 expression does not correlate with patient survivorship, and their inhibition does not block the growth of synovial sarcoma cultures in vitro [98, 100, 119, 124].

Fibroblast Growth Factor Pathway

Fibroblast growth factor (FGF) signaling is critical for synovial sarcoma growth. Human and murine cells transfected with *SS18–SSX* are enriched with genes of the FGF signaling system [8, 19, 61, 84, 120]. Beside occasional alterations in the levels of *FGFs* and *FGFRs*, *FGF18*, *FGFR2*, and *FGFR3* are constantly upregulated in the disease [57, 58, 106, 107, 118, 121, 133]. SS18–SSX targets *FGFR2* and hampers BMI1-mediated transcriptional repression [8]. Synovial sarcoma tissues and cell lines stain positive for FGF8, FGF18, and multiple FGFRs, some of which are also retrieved from cultured *SS18–SSX*-positive cell lysates [123, 129, 133]. The addition of recombinant FGF8 or FGF2 enhanced the growth of serum-deprived synovial sarcoma cultures [133]. FGFR inhibition seems to impede the proliferation of synovial sarcoma cells and others expressing *SS18–SSX* in vivo and in vitro [8, 123, 133].

Hepatocyte Growth Factor Pathway

The hepatocyte growth factor (HGF) pathway may be potentially important in the tumorigenesis of a small number of synovial sarcomas at best. Indeed, aside from one study, all gene expression microarray investigations of synovial sarcoma and *SS18–SSX*-positive cells revealed downregulated *HGF* and *HGFR* compared with other soft-tissue malignancies and *SS18–SSX*-negative cells [8, 19, 58, 61]. *HGF* and *HGFR* mRNAs are isolated in 53.3% and 66.7% of synovial sarcoma specimens, respectively [43, 134]. A recent sequencing profiling analysis identified *HGFR* gene amplification in one of 19 (5.3%) cases [135]. HGF is immunoreactive in 31.9% to 68.4% of tumor specimens and associates with worse survival [134, 136–138]. Despite lacking a prognostic value in the disease, HGFR expression is highly variable, ranging between 0 and 90.5% [43, 119, 134–139]. At baseline, few *SS18–SSX*-positive cells are positive for phosphorylated HGFR, secrete HGF in their culture medium, and depend on the HGF/HGFR circuit to enhance their in vitro proliferation, invasion, and chemoresistance, as well as their complete transformation in xenografted mice [119, 130, 139, 140]. Albeit specific to select synovial sarcoma cells, this aggressive phenotype is largely reversed upon HGFR inhibition [139].

Insulin Growth Factor Pathway

Translational investigations report a functional insulin growth factor (IGF) network in synovial sarcoma, which is yet to be corroborated clinically. In contrast to the variable expression of most *IGFRs* and *IGFBPs*, *IGF1*, *IGF1R*, *IGF2*, and *IGFBP2* are consistently upregulated in *SS18–SSX*-positive cells [8, 19, 57, 58, 61, 84, 120, 121, 141–144, 145•]. Apoptosis of serum-depleted synovial sarcoma cell lines is prevented with IGF1 addition to monolayer cultures [88]. SS18–SSX peptides promote tumor formation by inducing *IGF2* transcription through mechanisms that involve SMARCA2 and SMARCA4 [19, 142]. Synovial sarcoma specimens and cell lines overexpress IGF2, the supplementation of which activates IGF1R and accelerates cellular growth in vitro [144, 145•, 146, 147]. Similarly, IGF1R is upregulated in synovial sarcoma samples and its expression is associated with an aggressive phenotype [128, 141, 144, 148]. IGF2 or IGF1R inhibition induced apoptosis, reduced migration, and delayed proliferation of *SS18–SSX*-positive rat cells and synovial sarcoma cell lines [142, 144]. Compared with other soft-tissue tumors, synovial sarcoma displays high IGFBP2 and

IGFBP7 immunoreactivity, the latter strongly predicting metastases [121, 149].

Platelet-Derived Growth Factor Pathway

The platelet-derived growth factor (PDGF) pathway is constantly activated in synovial sarcoma. Mutational anomalies affecting *PDGF*s and *PDGFR*s are rarely documented in the disease [92, 128, 150]. RT-PCR and gene expression profiling of *SS18–SSX*-positive cells revealed a unique and consistent overexpression of *PDGFRA*, *PDGFA*, and *PDGFB*, with a concomitant downregulation of *PGDFRB* [8, 57, 58, 60, 61, 92, 107, 120, 128, 151]. In almost all synovial sarcoma cases and cell lines, immunohistochemistry, immunoprecipitation, Western Blot, and phosphoproteomic array analyses were frequently positive for either one of the phosphorylated PDGFRs and their respective cognate ligands, PDGFRA and PDGFA most frequently [92, 119, 128–130, 135, 150, 151]. A potential link between *SS18–SSX* oncofusions and PDGFRA has been suggested, but its clinical implications are still preliminary [119, 128, 139].

Stem Cell Factor Pathway

The activity of the stem cell factor (SCF) pathway is variable in synovial sarcoma and may be fundamental in a subset of tumors. Although gene expression profiling reported *SCFR* repression as characteristic for this tumor, both *SCF* and *SCFR* mRNAs are found in at least 80% of cases [43, 58, 151]. Sanger DNA sequencing identified an *SCFR* mutation in at least 5% of cases [135]. SCF expression has not been assessed in synovial sarcoma, whereas SCFR staining varied broadly, with some studies showing a complete absence of this marker and others reporting positive rates as high as 100% [43, 92, 99, 100, 150–153]. Protein extracts retrieved from 40 synovial sarcomas were only positive for the phosphorylated isoform of SCFR in 18 (45%) tumors [151].

Vascular Endothelial Growth Factor Pathway

Emerging evidence suggests an active vascular endothelial growth factor (VEGF) pathway in synovial sarcoma, the significance of which remains a subject of debate. Except for *VEGFA*, *VEGF*s are downregulated in synovial sarcoma samples and *SS18–SSX*-expressing cells [8, 19, 57, 58, 116]. To date, few mutations involving only *VEGFR2* have been reported in the disease [10, 135]. At the protein level, both VEGFA and VEGFR2 are detected in cellular cultures and tumors derived from mice injected with synovial sarcoma cells [116, 129]. Clinically, 23 of 25 (92%) specimens stained positive for VEGFA, which correlated with spheroid formation in soft-agar assays [116].

Developmental Pathways

Hippo Pathway

Data regarding the Hippo network in synovial sarcoma is still emerging, but current evidence advocates a nuclear accumulation of the transcriptional coactivators YAP and TAZ as a result of a repressed signaling pathway in the disease. Despite being consistently reduced in human specimens and *SS18–SSX*-positive cells, *YAP*, *TAZ*, *TEAD3*, and *TEAD4* seem sequestered within the nuclei of at least 75% of synovial sarcoma tissues and cell lines [19, 58, 145•]. A functional link has been even suggested between *SS18–SSX* and the nuclear relocation of these peptides, the inhibition of which prohibited cellular growth by apoptosis induction [112, 145•].

Notch Pathway

Multiple effectors of the Notch signaling network are differentially upregulated in synovial sarcoma, but data is currently lacking to suggest a causative role for this pathway in the growth or maintenance of the disease. Apart from one study showing a repressed *JAG2*, all investigations found an induction of the expression of *NOTCH1*, *NOTCH3*, *JAG1*, *JAG2*, *DLL1*, *HEY1*, and *HES1* in murine and human myofibroblasts transfected with *SS18–SSX2* [8, 19, 60, 61]. Similar findings have been documented in human specimens of synovial sarcoma using oligonucleotide and gene array analyses [8, 57, 58, 154].

Sonic Hedgehog Pathway

Preliminary findings support a role for the Sonic Hedgehog signaling pathway in synovial sarcomagenesis. Mediators of this network, including *SHH*, *PTCH1*, *SMO*, and *GLI2*, have been regularly overexpressed in murine and human mesenchymal cells expressing *SS18–SSX2*, as well as synovial sarcoma specimens and xenografts [8, 57, 58, 112]. Chromatin immunoprecipitation sequencing revealed both *Gli2* and *Shh* loci to be highly enriched for *SS18–SSX2* in transfected C2C12 murine myoblasts, but no specific consensus sequence that predicts SS18–SSX binding has been isolated to date [8].

Wnt Pathway

There is a substantial body of evidence to implicate the Wnt network in the pathogenesis of synovial sarcoma. This disease harbors rare sporadic mutations in Wnt-related genes, including *APC*, *AXIN*, *CTNNB1*, and *TLE2* [9, 92, 94, 108, 109, 111, 112, 115, 155, 156]. Genome-wide profiling and mRNA analyses of surgical specimens and *SS18–SSX*-positive cells revealed an upregulation of *WNT*s, *FZD*s, *LRP*s, *AXIN*s, *TLE*s, *TCF*s, and *LEF*s, encoding some of the proteins that comigrated with the synovial sarcoma fusions to specific promoter loci [8, 19, 54, 57,

58, 60, 61, 107, 112, 118, 120, 154, 157, 158]. At least half of synovial sarcoma samples and *SS18–SSX*-expressing cells display evidence of nuclear β-catenin expression, which oftentimes predicted worse patient outcomes [54, 61, 91, 94, 108, 112, 114, 115, 159]. In this disease, Wnt effectors and antagonists are predominantly overexpressed and repressed, respectively [94, 107, 118, 135, 157, 160, 161].

A partial transcriptomic overlap was detected between murine fibroblasts expressing *SS18–SSX1* and their controls stimulated by Wnt3a [61]. *CTNNB1* depletion resulted in cell proliferation arrest and apoptosis induction in synovial sarcoma cell lines, complete sarcomagenesis abrogation in mice injected with *SS18–SSX2* Myf5 myoblasts, and size reduction of generated tumors [94, 112]. This behavior correlated with a membranous relocation of β-catenin and subsequent cytoplasmic protrusions, phenotypes reminiscent of adhesion properties acquisition [112]. Similar findings were obtained with *FZD10* and *TLE1* inhibition, which hinder anchorage-dependent and independent growth while promoting apoptosis in synovial sarcoma [56, 118, 158, 160].

Therapeutic Challenges and Perspectives

Despite substantial advancements in the understanding of synovial sarcoma, much remains to be elucidated. The tumor-initiating cell of this disease is still undetermined, but mounting evidence suggests a mesenchymal origin [4–8]. However, aside from one conditional mouse model claiming a myoblastic lineage for synovial sarcoma, details regarding the exact type of the mesenchymal cell are still lacking, as this cellular subgroup is highly heterogeneous, and identical experiments in different cell types could yield divergent results [8, 120, 162]. Moreover, in vitro studies utilize genetically altered and immortalized cells that do not really reflect the human cellular pathophysiology, making the translation of the molecular results into clinical practice at least partially compromised [163]. Most in vivo analyses investigate the disease at a specific time during its course, without evaluating its progression. Addressing the latter question might elucidate the role of each dysregulated gene in synovial sarcoma (primary or secondary event for early sarcomagenesis or tumor maintenance, respectively).

Deciphering the operational mechanisms by which SS18–SSX oncoproteins promote sarcoma formation is challenging. One may speculate that the functions of the preserved domains in the final translocation recapitulate those of its native components; however, this may not always hold true. Genetic anomalies do not always explain proteomic alterations, as evidenced by most molecules being overexpressed despite their respective genes' wild-type status [9, 10, 92, 94, 108–113, 115, 126–128, 135, 150, 155, 156]. Also, pooled expression level is not an inevitable direct measure of a network's activity and susceptibility and may not seem as important as the compartment in which the protein is localized, as shown by the nuclear accumulation of YAP/TAZ (Hippo) and β-catenin (Wnt) [54, 61, 94, 112, 145].

As with other translocation-associated soft-tissue malignancies, the optimal therapeutic approach in synovial sarcoma consists of selectively targeting the initiating driver fusion, which consistently affects multiple functional oncogenic signaling networks in the disease [8, 20, 54, 56, 59, 61, 70, 87, 88, 94, 95, 104, 112, 116, 128, 142, 145, 158]. While short interfering RNAs hold the promise to nullify the translocation, this strategy seems limited with regard to delivery and stability [164]. SS18–SSX peptides could be also potentially dismantled using proteolysis-targeting chimeras (PROTACs), a proteasomal degradation technology that has been associated with some success in murine and human preclinical tumoral models [165•]. Alternatively, emerging preclinical evidence suggests that inhibition of SWI/SNF and Polycomb complexes via depletion or tagging of critical components for ubiquitination may be an attractive therapeutic strategy in synovial sarcoma [56, 59, 70, 158, 165•, 166, 167•, 168••, 169]. Clinical trials employing these therapeutic avenues are summarized in Table 1.

Tailored therapies in synovial sarcoma are also challenged by the tumor's resistance and escape mechanisms, stemming from the redundancy of its operational pathways (Fig. 3). To optimize the chances for positive treatment response in the future, it may be beneficial to perform a tumoral gene profiling

Table 1 Investigational trials exploring inhibitors of the SWI/SNF and Polycomb complexes in recurrent or metastatic synovial sarcoma

Clinical trial	Trial phase	Status	Drug tested	Drug class	Condition	Results
NCT02601937	Phase 1	Recruiting	Tazemetostat	EZH2 inhibitor	Relapsed or refractory SMARCB1-negative tumors or synovial sarcoma	Not available
NCT02875548	Phase 2	Recruiting	Tazemetostat	EZH2 inhibitor	Advanced synovial sarcoma	Not available
NCT00112463	Phase 2	Complete	Romidepsin	HDAC inhibitor	Metastatic or unresectable synovial sarcoma	Not available
NCT01136499	Phase 2	Complete	Panobinostat	HDAC inhibitor	Advanced metastatic or unresectable synovial sarcoma	No responses in six patients
NCT01879085	Phase 2	Recruiting	Vorinostat	HDAC inhibitor	Metastatic or unresectable synovial sarcoma	Not available
NCT00937495	Phase 2	Complete	Vorinostat	HDAC inhibitor	Advanced, unresectable, or metastatic synovial sarcoma	Not available

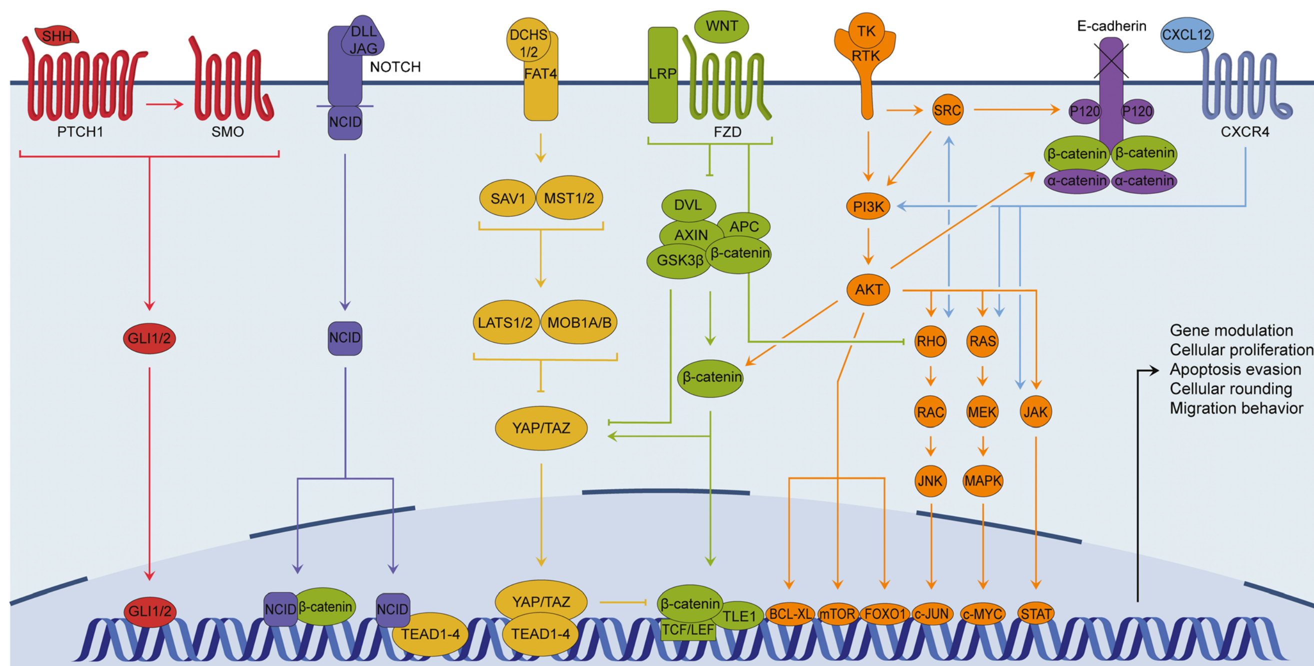

Fig. 3 Operational signaling landscape in synovial sarcoma. Blunted arrows (⊥) indicate inhibition whereas pointed arrows (➔) imply induction. The function of multiple signaling pathways is altered in synovial sarcoma, including the Sonic Hedgehog (red), Notch (dark blue), Hippo (yellow), Wnt (green), receptor tyrosine kinases (orange: RTK [Eph, EGFR, FGFR, HGFR, IGFR, PDGFR, SCFR, VEGFR]), cadherins (purple), and chemokines (light blue). An extensive cross-talk exists between all networks, which may confer pathway co-dependencies with a resulting tumoral cell drug resistance to most common monotherapies used in clinical practice. Of particular relevance are the inter-network communications between the Wnt (β-catenin), Hippo (YAP/TAZ), and RTK (AKT) signaling pathways.

at diagnosis, followed by a simultaneous depletion of active networks, key complexes, and compensatory nodal proteins. This might explain, at least partially, the therapeutic benefit associated with pazopanib, a multi-receptor tyrosine kinase (RTK) inhibitor, in improving the survival of patients with advanced synovial sarcoma [170–172].

Conclusions

Synovial sarcoma is a karyotype-stable soft-tissue malignancy that carries few additional genetic anomalies. This disease is driven by an *SS18–SSX* translocation and seems to originate from a complicated, yet delicate, equilibrium between epigenetic activating and repressing multicomplexes that redirect the tumor's cellular machinery while charting a new neoplastic signaling landscape. Most recent advances stem from in silico or in vitro experiments, preventing a comprehensive adoption of the findings in clinical practice. Individual pathway repression has not proven effective in the disease, and therefore, a synergistical approach that targets multiple key pathways, complexes, and proteins, seems warranted.

Code Availability Not applicable.
Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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