Synovial Sarcoma: Recent Discoveries as a Roadmap to New Avenues for Therapy

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ABSTRACT

Oncogenesis in synovial sarcoma is driven by the chromosomal translocation t(X;18; p11;q11), which generates an in-frame fusion of the SWI/SNF subunit SS18 to the C-terminal repression domains of SSX1 or SSX2. Proteomic studies have identified an integral role of SS18-SSX in the SWI/SNF complex, and provide new evidence for mistargeting of polycomb repression in synovial sarcoma. Two recent in vivo studies are highlighted, providing additional support for the importance of WNT signaling in synovial sarcoma: One used a conditional mouse model in which knock-out of β-catenin prevents tumor formation, and the other used a small-molecule inhibitor of β-catenin in xenograft models.

Significance: Synovial sarcoma appears to arise from still poorly characterized immature mesenchymal progenitor cells through the action of its primary oncogenic driver, the SS18-SSX fusion gene, which encodes a multifaceted disruptor of epigenetic control. The effects of SS18-SSX on polycomb-mediated gene repression and SWI/SNF chromatin remodeling have recently come into focus and may offer new insights into the basic function of these processes. A central role for deregulation of WNT-β-catenin signaling in synovial sarcoma has also been strengthened by recent in vivo studies. These new insights into the biology of synovial sarcoma are guiding novel preclinical and clinical studies in this aggressive cancer.

CLINICAL FEATURES

Synovial sarcoma is an aggressive neoplasm that accounts for 10% to 20% of soft-tissue sarcomas in the adolescent and young adult population (1). Although it is typically diagnosed in young adults (median age 35), the age range is between 5 and 85 years (2). There is a slight male predilection (M:F ratio 1.13); 70% of cases present in the extremities, and the most common pattern of metastatic spread is to the lung (3). The mainstay of treatment is wide surgical excision with adjuvant or neoadjuvant radiotherapy, which provides a good chance of cure for localized disease. However, the disease is prone to early and late recurrences, and 10-year disease-free survival remains on the order of 50% (3). Synovial sarcoma is moderately sensitive to cytotoxic chemotherapy with agents such as ifosfamide and anthracyclines (4, S).

THE SS18–SSX FUSION ONCOGENE

Synovial sarcoma is uniquely characterized by the balanced chromosomal translocation t(X;18; p11;q11), demonstrable in virtually all cases (2), not found in any other human neoplasms. This translocation creates an in-frame fusion of the SS18 gene to SSX1 or SSX2 (6), whereby all but the carboxy terminal (C-terminal) 8 amino acids of SS18 become fused to the C-terminal 78 amino acids of the SSX partner (Fig. 1). An analogous translocation of SSX4 is detected in less than 1% of cases (7).

Multiple lines of evidence implicate SS18-SSX as the central genetic “driver” in this cancer: (i) its presence as the sole cytogenetic anomaly in up to a third of cases (8), (ii) the low frequency of additional mutations (9), (iii) its preservation in metastatic and advanced lesions (8), (iv) the death of synovial sarcoma cells upon SS18-SSX knockdown (10), and (v) its ability to induce tumors in conditional mouse models with appropriate histology, gene expression, and immunophenotype with 100% penetrance (11).

Functional Studies of SS18–SSX

Initial functional studies of SS18–SSX used yeast two hybrids and GAL4 fusion constructs, in which the relevant protein domains are fused to the DNA-binding domain of GAL4. These studies showed that SS18 is a transcriptional coactivator and that C-terminal SSX domains mediate repression (12, 13). The fusion oncoprotein thus contains both...
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activating and repressing domains, although neither partner has a DNA-binding domain. Several other putative binding partners were also identified as shown in Fig. 1, but the mechanisms targeting the fusion protein to specific DNA regions were elusive until recently.

**SS18 and SS18-SSX Incorporate into the SWI/SNF Complex**

Thaete and colleagues (14) showed association of both SS18 and SS18–SSX with the DNA-dependent ATPase BRM, the catalytic subunit of SWI/SNF chromatin remodeling complexes. Subsequently, Kato and colleagues (15) showed that SS18 is a stable and integral component of SWI/SNF complexes using communoprecipitation and mass spectrometry in nuclear extracts of HeLa cells. Middeljans and colleagues (16) extended these results by showing that the fusion oncprotein is similarly incorporated into stable SWI/SNF complexes. All commonly observed subunits were recovered in reciprocal purifications between tandem affinity purification-tagged SS18–SSX1 and other subunits, indicating minimal perturbation of the core complex when the fusion oncogene is stably expressed in HEK293 cells. Kadoch and Crabtree (17) observed high-affinity binding of both SS18 and SS18–SSX to the core subunits of SWI/SNF, and immunodepletion of nuclear extracts showed undetectable levels outside of this association. In contrast with the results of Middeljans and colleagues (16), these authors observed that expression of the fusion oncogene induced depletion of the BAF47 (SMARCB1) subunit from the SWI/SNF complex in experiments using transiently expressed GFP-tagged SS18–SSX in an HEK293 background. The authors also reported SMARCB1 loss in synovial sarcoma cell lines, noting that siRNA knockdown of SS18–SSX restored SMARCB1 inclusion in SWI/SNF complexes.

Both studies suggest that SMARCB1’s association with SWI/SNF may be more labile than for other subunits, and it is conceivable that SMARCB1 is displaced from SWI/SNF by aberrant protein interactions involving SS18–SSX. Alternatively, SMARCB1 may be stabilized in SWI/SNF complexes by unknown binding partners in different experimental conditions (e.g., transduced vs. transfected HEK293 cells, or differences in the parent HEK293 cell lines, which have complex genomes and known clonal heterogeneity). HEK293 cells, although convenient for transfection and at least partially permissive for (short-term) SS18–SSX expression, may not represent the most relevant cell line model as discussed in the Cellular Background for SS18–SSX Oncogenesis section, below. Resolution of these conflicting results will have important implications because SMARCB1 (aka SNF5, INI1) is a known tumor suppressor, with homozygous loss in 98% of rhabdoid tumors (18), 90% of epithelioid sarcomas, and more than half of myoepithelial carcinomas (19). If SMARCB1 loss contributes to oncogenesis in synovial sarcoma, advances in the study of SWI/SNF–directed therapies in rhabdoid tumors may have direct translational implications. Of potential importance, synthetic lethalties may be explored by analogy to rhabdoid tumors, where, for example, tumorigenesis was found to depend on functional BRG1 in the residual SWI/SNF complex (20). Although caution is currently indicated in drawing simple parallels with rhabdoid tumors, these proteomic studies imply that the mechanisms of SS18–SSX-mediated oncogenesis are intimately related to dysregulation of SWI/SNF chromatin remodeling.

SWI/SNF functions to reposition nucleosomes on genomic DNA, and can also promote nucleosome disassembly and histone exchange (reviewed in ref. 21). The canonical activity of SWI/SNF is to create nucleosome-depleted regions at core promoters and regulatory regions, facilitating transcription factor access to DNA. SWI/SNF activity is broadly recruited across the genome to effect switches in chromatin state and gene expression.
review the importance of this complex in tumor suppression. However, the specific mechanisms of tumor suppression remain elusive, due to the diverse and tissue-specific roles of the complex in transcriptional regulation.

SMARCBI and BRG1 inactivation lead to increased proliferation (23), at least in part due to impaired transcriptional activation of the CDKN2A/B tumor suppressors (24). This result has been related to the requirement of SWI/SNF activity for the eviction of repressive polycomb complexes from chromatin, and highlights the general principle of antagonism between SWI/SNF and polycomb activities. In this regard, the dominance of polycomb repression would have profound implications for the regulation of stemness and differentiation, and may prove to be a central aspect of oncogenesis in SWI/SNF–mutated tumors. Other mechanisms of SWI/SNF oncogenesis have been elaborated, including mutations in ARID1A, where it has been suggested that functional SWI/SNF is required to execute the p53 transcriptional response (25). Although not shown in synovial sarcoma, such an effect may explain the lack of TP53 mutation in the majority of these lesions. SWI/SNF dysfunction also compromises DNA double-strand break repair, and may confer sensitivity to DNA-damaging agents (26); this may contribute to the sensitivity of synovial sarcoma to radio- and anthracycline therapies.

SS18–SSX and Epigenetic Transcriptional Repression

Whereas SS18, through its interactions with the SWI/SNF complex, might be expected to have a role in transcriptional activation, its fusion partner SSX associates with the polycomb repressor complex, which has opposing effects. An early observation was that SS18–SSX localizes at discrete nuclear foci within BM11-labeled polycomb bodies (27). More recently, chromatin immunoprecipitation sequencing (ChIP-Seq) results from HA-FLAG–tagged SS18–SSX, expressed in transfected C2C12 mouse myoblasts (28), correlated SS18–SSX binding with polycomb-marked nucleosomes (trimethylated histone H3K27) at a subset of genomic H3K27me3 sites. In studies investigating possible target genes for SS18–SSX-mediated repression, expression profiling (29) showed the tumor suppressor EGR1 to be among the most consistently downregulated genes in synovial sarcoma. ChIP studies revealed the presence of SS18–SSX at a cyclic AMP response element (CRE) in the EGR1 promoter (30). Furthermore, inhibitors of histone deacetylases (HDAC)—whose antican-cer activity had been shown previously in synovial sarcoma xenografts (31)—were found to reverse the repression of EGR1, accompanied by loss of polycomb residency at this locus.

Subsequent studies detailed proteomic and biochemical characterizations of SS18–SSX-binding partners, and identified Activating Transcription Factor 2 (ATF2) as the transcription factor responsible for targeting the fusion oncoprotein to CRE sites (32). Moreover, these studies identified a robust interaction of the transcriptional corepressor Transducin-Like Enhancer of Split 1 (TLE1) with the SSX portion of the fusion oncogene in human and mouse model syno-vial sarcoma cells, confirmed in surgically excised patient tumor tissue. SS18–SSX serves as a bridge between ATF2 and TLE1, mediating repression of ATF2 targets, including among others EGR1, ATF3, and CDKN2A. Both the SWI/SNF component BRM and the polycomb component EZH2 were observed to coelute with the SS18–SSX oncoprotein. Reciprocal immunoprecipitations showed copurification of core PRC2 subunits EZH2, SUZ12, and EED with TLE1, SS18–SSX, and ATF2, indicating the presence of a stable repressive complex nucleated by the fusion oncoprotein. ChIP and electrophoretic mobility shift assays confirmed the presence of this repressive complex at conserved CRE elements in ATF2 target gene promoters. Treatment with HDAC inhibitors disrupts this complex (32).

TLE family proteins are corepressors of WNT target genes (33) and effectors of HES-mediated NOTCH repression (34), and are highly expressed in a number of embryonic progenitor fields where these pathways are known to regulate self-renewal and stemness. The identification of the corepressor TLE1 as an SS18–SSX-interacting protein is also significant because expression profiling experiments have identified TLE1 as among the most consistently highly expressed genes in primary synovial sarcoma specimens (29, 35). Incidentally, nuclear expression of TLE1 is readily detectable by immuno-histochemistry on formalin-fixed paraffin-embedded tissues, and its diagnostic value for synovial sarcoma has been confirmed (36, 37), leading to its adoption into clinical use.

THE CELLULAR BACKGROUND FOR SS18–SSX ONCOGENESIS

The above findings contribute to knowledge about SS18–SSX target genes and/or the cellular background in which the oncogene operates, but do not clear up enduring mysteries about the true cell of origin for synovial sarcoma or its line of differentiation. Despite the name, synovial sarcoma is not derived from synovium, nor does it differentiate into synovial-type tissue. The term synovial sarcoma is actually a misnomer—true mesenchymal–epithelial transition, with formation of internal epithelial surfaces and even glandular structures. This epiphenomenon is driven by variable repression of E-cadherin by SS18–SSX interactions with the SNAIL and SLUG transcription factors (38). The predominant mesenchymal component in synovial sarcoma can grow as a pure sheet of plump spindle cells reminiscent of embryologic mesenchyme, but can alternatively display variable degrees of multilineage mesenchymal differentiation (39), with some cases producing loosely myxoid, densely collagenized, or even osteoid-type extracellular matrix.

An intriguing observation whose relevance to the cell of origin of synovial sarcoma remains unclear came from the discovery that a mouse model of monophasic synovial sarcoma do indeed display unusual morphologic features that are suggestive of a capacity for pluripotential differentiation. Whereas approximately 75% of cases are “monophasic” spindle cell tumors, the less common biphasic variant constitutes a pathognomonic example of true mesenchymal–epithelial transition, with formation of internal epithelial surfaces and even glandular structures. This epiphenomenon is driven by variable repression of E-cadherin by SS18–SSX interactions with the SNAIL andSlug transcription factors (38). The predominant mesenchymal component in synovial sarcoma can grow as a pure sheet of plump spindle cells reminiscent of embryologic mesenchyme, but can alternatively display variable degrees of multilineage mesenchymal differentiation (39), with some cases producing loosely myxoid, densely collagenized, or even osteoid-type extracellular matrix.
required. Expression in later stage MYF6+ myoblasts caused myopathy but no tumors, whereas cleavage-stage embryo expression or conditional expression in earlier (PAX3+ or PAX7+) myoblast populations was embryonic lethal, as was expression of SS18–SSX2 in early ectoderm (AP2+), bone/cartilage (SOX9+), endothelial (FLK1+) or neural (Nestin1+) precursor populations (40). However, a tamoxifen-induced conditional expression model leads to development of less aggressive synovial sarcomas in a somewhat different anatomical distribution (including paraspinal and facial primary sites), suggesting that backgrounds other than MYF5+ myoblasts may also be permissive for SS18–SSX oncogenesis. Notably, neither in mouse models nor in human tissues do the synovial sarcoma tumors express biomarkers typical of muscle differentiation.

Whereas expression of SS18–SSX in most cellular backgrounds appears to precipitate cell death, pluripotential stem cells as well as human mesenchymal stem cells are permissive—although importantly the expression profiles induced by SS18–SSX in these two precursor populations are very different (41). HEK293 cells can also be successfully engineered to express SS18–SSX, but as mentioned above, different oncoprotein complexes appear to be formed in transient transfection versus stably transfected models. In this regard, the high levels of TLE1 observed in synovial sarcoma may be crucial, considering its possible central role in recruiting repressive activities to target promoters. Expression of TLE1 and its interacting transcription factors in stem/progenitor cells may help define permissive lineages for the development of tumors in transgenic animals. These observations highlight a major limitation of most engineered models of synovial sarcoma—the cellular background is probably not correct. Therefore, it is critical that experimental findings attributed to synovial sarcoma biology from experimental systems are verified in models derived from primary human tumor tissue expressing SS18–SSX under its endogenous promoter. These include several published cell lines grown as monolayers, 3D spheroids (42) or xenografts (43). Results ultimately will have to be verified on patient tumor samples. Methodologically, verification of SS18–SSX fusion transcript expression is an important way to confirm model or tissue integrity in synovial sarcoma research.

**Secondary Mutations in Synovial Sarcoma**

In keeping with the observed chromosomal stability, the most commonly mutated gene in human cancer, TP53, is rarely mutated in synovial sarcoma, occurring in 11 of 92 cases across three published studies (46–48); in these studies, copy-number gains in the p53-suppressing oncogene MDM2 were somewhat more frequent. Overall, wild-type p53 appears to be retained in most synovial sarcomas, although its function may be impaired through upstream regulatory events, as in several well-described prosurvival interactions within the AKT–PTEN pathway.

Otherwise, targeted sequencing approaches have highlighted mutations in PTEN, CTNNB1, and APC in 8% to 14% of cases (49–51), providing some support for oncogenic activation of the AKT–mTOR and WNT signaling pathways in this sarcoma (see below).

As of this writing, only one whole-exome sequencing study had been published on synovial sarcoma, on tumors from 7 patients (9). This work identified an average of eight somatic mutations per tumor exome, and no genomic losses in the majority of cases. Solitary mutations in cancer pathway genes were identified for TP53, SETD2, and FBXW7.

On the whole, these results suggest an encouraging setting for targeted therapy of synovial sarcoma—if treated early in its natural history, when the majority of tumors do not exhibit genomic instability or extensive genomic rearrangements. Cell death pathways and growth controls may be largely intact and responsive to effective targeting of SS18–SSX. Compared with most common cancer types, there may be fewer escape mechanisms for emergence of therapy-resistant subclones in synovial sarcoma.

**Gene and Protein Expression in Synovial Sarcoma**

A major theme from gene-expression profiling studies of synovial sarcoma relates to high expression of mediators involved in the patterning systems of early embryogenesis, including WNT (LEF1, AXIN2, WIF1, WNT5A, and FZD10), NOTCH (HES1, JAG1, JAG2, and NARP), Hedgehog (PTCH1, GLI1, and GLI2), FGF (FGFR2, FGFR3, FGF18, and FGF9), and BMP pathways (BMP7, BMP5, BMPR2, and SOSTDC1). These results and expression of other markers of embryonic primordia (SALL2, TLE1, SIX1, SIX4, and DLX2) support the idea that synovial sarcoma cells have a stem-like or early progenitor phenotype. Of note, primary synovial sarcomas show a remarkable correspondence with the expression profiles of the conditional MYF5–CRE mouse model (11) and SS18–SSX-transduced embryonic stem cells (41).

Synovial sarcomas commonly express relatively high levels of mRNA for cancer–testis antigens, a group of potentially immunogenic proteins expressed in many tumor types, but not in normal adult tissues outside the germline: PRAME, CTAG1A (encoding NY-ESO-1), and MAGEE1 are prominent examples. The possible relevance of this aberrant antigen expression in terms of response in recently developed immunotherapy approaches remains to be determined.

High expression of neural (NPTX2, NEFH, and NTNG2) and chondrocyte (COL2A1, COL9A3, SOX9, and TRPS1) lineage markers has been interpreted as consistent with differentiation from neural crest progenitors. High mRNA expression in PEN2 and NTNG2, which are not expressed in normal adult tissues, further strengthens this notion.
of SOX2, an important determinant of neural progenitors and embryonic stem cells, is common in synovial sarcoma and has been shown to be critical for growth of some cell lines in vitro (15, 39). However, its expression is absent in other cell lines and is not a universal feature of primary tumor specimens.

Other notable features of the synovial sarcoma profile include differential high expression of BCL2, as well as of the receptor tyrosine kinases (RTK) PDGFRα, EGFR, and ERBB2. The latter group may be important for the stimulation of PI3K–AKT signaling, which has been reported as critical to synovial sarcoma viability in several studies (52, 53), and is discussed further below.

Many of the above findings have been confirmed at the protein level in patient specimens, including FZD10 (54), HES1 (55), NY-ESO-1 (56), SALL2 and EGFR (58), BCL2 (59), SOX9 (60), FGFRs and their receptors (61), PDGFRα (52), and WNT pathway mediators (discussed further in the next section).

**TARGETABLE ONCOGENIC PATHWAYS ACTIVE IN SYNOVIAL SARCOMA**

**WNT–β-Catenin Signaling Pathway**

There has been longstanding evidence for WNT activation in a subset of synovial sarcomas. Sanger sequencing studies found canonical activating mutations in CTNNB1, at frequencies of 4% (N = 24; ref. 62), 8% (N = 49; ref. 63), and 12% (N = 16; ref. 50), and APC mutations in 8% (N = 49) of cases (51). At the protein level, WNT pathway activation, as evidenced by nuclear accumulation of β-catenin, has been studied using immunohistochemistry. By this method, nuclear accumulation of β-catenin is detected in 30% to 60% of synovial sarcomas (64, 65), primarily in monophasic cases or in the spindle cell component of biphasic cases. The SYO-1 synovial sarcoma cell line harbors a codon 34 mutation in CTNNB1 (G34L) with concomitant protein accumulation and shows reduced proliferation and impairment in standard invasion and migration assays when transfected with an inhibitory dominant-negative LEF1 construct (T. Saito and colleagues, unpublished data).

Recently, two independent studies have provided important functional evidence for a critical role of this signaling pathway in synovial sarcoma. Barham and colleagues (66) showed that genetic loss of β-catenin blocks tumor formation in the MYF5–CRE SS18–SSX2 transgenic model described above. To confirm this observation in the human setting, they showed that pharmacologic activation of CSNK1A by pyrvinium, known to inhibit β-catenin signaling, or RNAi knockdown of LRPI6 could both impair growth of human synovial sarcoma cell lines. These investigators also showed that SS18–SSX can induce nuclear β-catenin accumulation, apparently by inducing autocrine signaling through its aberrant transcriptional effects. These data may explain the fact that the proportion of human synovial sarcoma tumors with nuclear β-catenin accumulation is several fold higher than the rate of CTNNB1 or APC mutations.

In a separate recent study, Trautmann and colleagues (67) found that introduction of SS18–SSX into HEK293 cells induced activation of WNT–β-catenin signaling. Conversely, small-molecule TCF–β-catenin complex inhibitors reduced cell viability in vitro in five human synovial sarcoma cell lines and reduced in vivo growth of xenografted SYO-1 synovial sarcoma cells.

Together, these studies nominate the WNT–β-catenin signaling pathway as an important new candidate therapeutic target in synovial sarcoma, with putative mechanisms as outlined in Fig. 2. As new agents efficiently targeting this pathway are in clinical development, these studies provide a critical preclinical rationale for their evaluation in clinical trials (68, 69). Beyond the direct targeting of WNT–β-catenin signaling pathway components by small molecules, targeting of key interacting proteins also offers therapeutic opportunities. For instance, β-catenin forms a complex with the transcriptional modulator YAP1 and the YES1 tyrosine kinase, which may explain why dasatinib, which blocks the latter, also inhibits WNT–β-catenin–dependent proliferation (69). Interestingly, a recent study found that dasatinib caused apoptosis and inhibition of cellular proliferation in synovial sarcoma cells; some data support that this effect is mediated by inhibition of activated SRC (70), but it is tempting to speculate that the potency of the drug may also have been due to concurrent effects on WNT–β-catenin–dependent targets.

In light of the recent finding that SS18–SSX may, under certain circumstances, displace SMARCB1 from SWI/SNF chromatin remodeling complexes (17), it is also notable that loss of SMARCB1 results in activation of WNT–β-catenin signaling in mouse and cell culture models, reflecting a role for the SWI/SNF complex in regulating this pathway (71).

**AKT–mTOR Signaling Pathway**

Various lines of evidence also support an important role for the AKT–mTOR pathway in synovial sarcoma, including genetic, protein level, preclinical, and clinical trial data. At the genetic level, PTEN mutations are found in only a minority of cases (49, 62, 72) and canonical PIK3CA mutations are even more uncommon (72). Nonetheless, several groups have demonstrated frequent activation of AKT in synovial sarcoma, and its dependency on upstream RTKs (53, 73, 74). As noted above, apoptosis induction in synovial sarcoma cell lines by HDAC inhibitors is at least partially dependent on derepression of EGR1 and subsequent induction of PTEN (30), a phenomenon that may help to identify strategic combinations involving these promising therapeutic agents.

Notably, fundamental interactions of PI3K–AKT–mTOR and RAS–MEK–ERK pathways have been identified downstream of RTK signaling, and multiple levels of feedback regulation have been identified within and between these pathways, as summarized in Fig. 3. These interactions underlie intrinsic resistance to PI3K–AKT–mTORC1-targeted monotherapies in synovial sarcoma, for example, involving feedback activation of AKT following mTOR inhibition, which can be mediated by either IGF1R or PDGFRα (43, 52). These data support the combination of mTOR inhibitors with inhibitors of particular RTKs that potentiate feedback AKT activation in a given tumor. Strategies that may intercept these signals at critical downstream nodes are also under investigation, including the combination of PI3K and MEK inhibitors, and the use of pan-mTOR kinase inhibitors targeting both mTORC1 and mTORC2 (which are not associated with reactivation of AKT; ref. 75).

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Antiapoptotic Pathways

Histologically, synovial sarcomas typically display few mitotic figures, while also displaying few apoptotic bodies. The tumor’s propensity in many cases for slow growth, late recurrences, and chemotherapy resistance is consistent with an antiapoptotic phenotype. A striking feature of synovial sarcoma is its consistently very high expression of BCL2 (59, 76, 77), but no evidence has been found that the BCL2 gene is a direct target for transcriptional upregulation by SS18–SSX; therefore, its high level of expression may be a secondary oncogenic effect, or may reflect a prerequisite cellular background to be permissive for SS18–SSX. In contrast, the BCL2 family members BCL2A1 and MCL1 are direct targets for SS18–SSX-mediated repression. Resistance to new BH3 mimetic BCL2 inhibitors in lymphomas is typically induced by activation of MCL1, but this escape mechanism is not available to synovial sarcomas, which appear to be highly sensitive to such drugs in human cells and an SS18–SSX2 mouse tumor model (78). These findings suggest that BCL2 inhibitors may be worth evaluating in synovial sarcoma, perhaps in combination with apoptosis-inducing cytotoxic chemotherapy, but as yet no such clinical trials have been opened.

CLINICAL TRIALS IN SYNOVIAL SARCOMA

Table 1 summarizes several trials in which synovial sarcoma may be included as an eligible diagnosis. Given its low incidence and a patient population split between pediatric and adult institutions, synovial sarcoma disease-specific trials have to date been largely precluded by logistical challenges. Instead, patients with this well-defined and unique sarcoma have generally been lumped with patients with other soft-tissue sarcomas, as in current trials of multitargeted TKIs (pazopanib: NCT02180867; regorafenib: NCT01900743). More closely tied to some of the biologic dependencies of synovial sarcoma...
Figure 3. Drug targets downstream of RTKs involved in synovial sarcoma. Extensive cross-talk and feedback regulation are observed in prosurvival signaling through MAPK–ERK and AKT–mTOR pathways. Intrinsic drug resistance to monotherapies can be mediated by activation of prosurvival signaling in either pathway, due to removal of inhibitory feedback (red lines). Drug targets discussed in the text are shown in green. BH3 represents proapoptotic BH3 domain-only proteins, and their activation by stress-activated protein kinases is shown (SAPK: JNK, p38). Dashed lines represent nuclear export and translation of mRNA to protein.
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Table 1. Summary data for clinical trials referenced in the text

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described above are efforts to test histone deacetylase inhibitors (including vorinostat: NCT01879085, NCT01294670) and IGF1R/mTOR inhibitor combinations (cixutumumab/tensirolimus: NCT01614795). Most of the above studies will incorporate preplanned disease-specific subgroup analyses, but most likely will remain severely underpowered to identify significant activity specifically against synovial sarcoma.

Inhibitors of the Hedgehog and NOTCH pathways are in earlier stages of development, but are already being tested in phase II studies that include synovial sarcoma among the eligible diagnoses (vismodegib + RO4929097: NCT01154452).

The first phase I trials of WNT inhibition in advanced solid tumors may constitute important referrals for synovial sarcoma. These include the agent PRI-724 that blocks the interaction of β-catenin with CBP (NCT01302405). Another new trial (NCT01351103) is of LGK974, an inhibitor of PORCN, an acyltransferase required for secretion of active WNT ligand; referral to this trial is contingent on demonstration of MHC antigen presentation. Given the unique and markedly mutated tumors, low expression of class I MHC, or to other immune suppression mechanisms active in mesenchymal cells with stem/progenitor phenotypes.

Expression of the WNT receptor Frizzled class receptor 10 (FZD10) is consistently high in synovial sarcoma, and the unlabeled antibody has only weak inhibitory activity against growth of MHC-I peptide vaccines, but may also relate to the generally observed lack of inflammatory infiltrates in synovial sarcoma. The basis of immune evasion in synovial sarcoma is unknown, but may be due to limited neoantigen production in these hypo-mutated tumors, low expression of class I MHC, or to other immune suppression mechanisms active in mesenchymal cells with stem/progenitor phenotypes.

Chimeric antigen receptor T cells represent another promising approach, in which T cells are engineered to express a chimeric T-cell receptor, whose signaling components are fused with an antibody fragment specific to a surface antigen on tumor cells. Activation of costimulatory signals is also engineered, so that the chimeric antigen receptor T cells are able to bypass immune checkpoints, recognizing and killing tumor cells independent of MHC antigen presentation. Given the unique and markedly elevated expression of FZD10 in synovial sarcoma, this would seem to represent an attractive target for this technology.

FUTURE PERSPECTIVES

Despite genomic and clinical progression, the SS18–SSX fusion gene is consistently retained in synovial sarcoma, and synovial sarcoma cells depend on continued SS18–SSX expression throughout the course of disease. This provides a basis for monitoring disease recurrence, through PCR detection of SS18–SSX expression.
therapeutic strategies. Finally, given the challenges involved in identifying additional epigenetic dependencies are expected to yield early-phase clinical trials. Screening experiments identify-inhibitors are under investigation in synovial sarcoma models critical oncogenic pathways it induces. In this regard, EZH2 inhibitors are under investigation in synovial sarcoma models and early-phase clinical trials. Screening experiments identifying additional epigenetic dependencies are expected to yield further mechanistic insights, which may guide additional therapeutic strategies. Finally, given the challenges involved in opening, accruing, and executing well-powered synovial sarcoma-specific trials, it is possible that drug-repurposing strategies will provide another set of opportunities for therapeutic advances. In cases where there is a good match between drug mechanism and oncogenic pathway, drugs developed for more common cancers may in fact work even better in a more genetically homogeneous malignancy like synovial sarcoma.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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