# Targeting Epigenetic Misregulation in Synovial Sarcoma

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**Like many sarcomas, synovial sarcoma is driven by a characteristic oncogenic transcription factor fusion, SS18-SSX. In this issue of *Cancer Cell*, Su et al. elucidate the protein partners necessary for target gene misregulation and demonstrate a direct effect of histone deacetylase inhibitors on the SS18-SSX complex composition, expression misregulation, and apoptosis.**

It has been more than 25 years since the recurrent translocation between chromosomes 18 and X in synovial sarcoma (SS) was first reported (Limon et al., 1986) and 18 years since the cloning of the productive fusion between *SYT/SS18* on chromosome 18 and *SSX* on chromosome X generated by this translocation (Clark et al., 1994). Although there have been great advancements in understanding the basic biology of this rare cancer, therapeutic strategies and clinical outcomes have remained largely unchanged since the 1980s, and large tumors, metastatic disease, and relapse are frequently impossible to control. In a new study, Su et al. (2012 [in this issue of *Cancer Cell*]) not only provide deep insight into the molecular mechanisms at work in SS but also suggest an unexpected explanation for the sensitivity of SS to histone deacetylase (HDAC) inhibition in preclinical models. Beyond helping to guide current clinical trials of HDAC inhibitors in SS, this study has implications for other transcription factor-fusion driven malignancies.

Sarcomas are a heterogeneous group of tumors of mesenchymal origin. Although representing less than 1% of adult neoplasms, they account for ~15% of all pediatric malignancies. As in leukemia and lymphoma, chromosome translocations that create oncogenic fusion proteins are common in sarcomas and are often pathognomonic for the particular sarcoma type (Davis and Meltzer, 2007). Interestingly, a large number of these fusion proteins involve transcription factors, and the misregulation of target gene expression is a clear driving mechanism of malignancy. SS contains fusions of the transcriptional coactivator SYT/SS18 with the SSX family of transcriptional corepressors (most frequently SSX1 or SSX2). The fusion protein typically contains nearly the entirety of SS18 and the C-terminal domains of SSX, which contain the strongest repressive activities (de Bruijn et al., 2007). Although the typical location near the synovial joints of the limbs gave rise to its name, SS occurs in many other sites, and in fact most likely originates in a myogenic progenitor compartment rather than synovial tissue (Haldar et al., 2007). SS are classified histologically as monophasic SS, in which all tumor cells exhibit a spindle cell morphology; biphasic SS, which contains a mixture of spindle cells and cells showing epithelial differentiation; and more rarely, poorly differentiated SS.

Su et al. (2012) began by identifying interactors of the endogenous SS18-SSX fusion protein in an SS cell line and immediately made two very important discoveries. The first reveals how SS18-SSX is recruited to specific genomic locations, an important unresolved question in the field because the fusion protein lacks direct DNA binding domains. Of interest, one interactor identified was the sequence specific transcriptional activator activating transcription factor 2 (ATF2). In follow-up experiments, the authors established that, at least for a set of important target genes, SS18-SSX is recruited directly to promoters by ATF2. The second important discovery was the interaction of SS18-SSX with the transcriptional corepressor transducin-like enhancer of split 1 (TLE1). High levels of TLE family members, especially TLE1, have been identified as potential biomarkers for SS (Terry et al., 2007), but their functional role in the disease has been unclear. The authors demonstrate that TLE1 serves as a bridge for tethering transcriptional repressors such as HDAC1 and PRC2 to SS18-SSX. Furthermore, the authors demonstrate for several genes normally activated by ATF2 that SS18-SSX recruits dominant repressive activities mediated by TLE1/HDAC1 and PRC2. Thus, an elegant model is developed to explain the effects of the SS18-SSX: targeting to DNA through the interaction of the SS18 moiety with the transcriptional activator ATF2 and recruitment of the repressive HDAC and PRC2 to ATF2 targets through the SSX portion of the fusion protein. At least for certain target genes, the repressive activities dominate, and aberrant gene repression contributes to the tumor phenotype. Consistent with this model, disruption of the complex by RNAi depletion of its components leads to target gene derepression and increased apoptosis. Perhaps most intriguing and of immediate therapeutic relevance is the discovery that HDAC inhibitor treatment disrupts the interaction between TLE1 and the fusion protein, thus releasing the HDAC and PRC2 complexes from ATF2 target promoters and derepressing target gene expression. While the mechanism could certainly be indirect, one possibility would be that either TLE1 or SS18-SSX is itself acetylated, thereby destabilizing the interaction. HDAC inhibitors are of significant clinical interest, with vorinostat and romidepsin now FDA-approved for treatment of cutaneous T cell lymphoma. Since they appear to target a core mechanism of SS, it is certainly plausible that this class of drugs will provide significant benefits to patients.

Although the new study firmly establishes these molecular mechanisms of the oncogenic fusion protein and the target genes investigated are certainly interesting ones, there is as yet no cohesive explanation of how normal progenitor cells are transformed by SS18-SSX. Which pathways are affected? Is it purely aberrant repression of pathways such as differentiation, cell death, and/or senescence that drive the disease? The glandular structures apparent in the biphasic subtype of SS suggest that the tumor is not characterized by a simple block of normal mesenchymal differentiation but raises the possibility that the cells are being driven into an aberrant state. A deeper dissection of the transcriptional networks misregulated by SSX18-SSX will be necessary to more fully understand the functional consequences of SSX18-SSX activity.

It is worth noting the relevance of these discoveries to other malignancies. Oncogenic fusions involving transcription factors is a common theme in malignancies of mesenechymal and hematopoetic lineages as well as in certain epithelial tumors such as prostate cancer. ATF, TLE, Polycomb, and HDAC family members have all been implicated in a wide array of cancer types through altered expression levels as well as somatic mutations. Perhaps most relevant to the SS results, endometrial stromal sarcoma (ESS) is often driven by fusions of the zinc finger transcription factor JAZF1 with Polycomb proteins SUZ12 or PHF1, or fusion of PHF1 and EPC1 (Chiang et al., 2011). Presumably, this leads to mislocalization of Polycomb complexes on the chromatin and misregulation of target genes. ESS has also been shown to be sensitive to HDAC inhibitors (Hrzenjak et al., 2008). While acute promyeloctic leukemia (APL) and SS are quite different diseases, the PML-retinoic acid receptor alpha (RARα) fusion which defines APL also functions largely through pathological recruitment of HDACs and PRC2 (Villa et al., 2007). In normal physiology the RARα switches between repressing target gene expression when retinoic acid (RA) levels are low and the receptor is unliganded and activating target gene expression when RA levels are high and bind the receptor. The oncogenic mechanism of the PML-RARα fusion is persistent association with corepressors regardless of physiological RA concentrations. The standard and typically successful treatment for APL is all-trans retinoic acid, which leads to release of corepressors from PML-RARα, derepression of target genes, terminal differentiation, and apoptosis.

The study of Su et al. (2012) is a significant addition to our understanding of the basic biological mechanisms of SS and highlights the commonly underappreciated role of transcriptional repression by oncogenic transcription factor-fusions. The phase I and II clinical trials for HDAC inhibitors in sarcoma currently underway, the outcomes of which are much anticipated, now have a stronger biological rationale and context for interpretation of their results. Most intriguingly, the effects of HDAC inhibitors on multiprotein complex composition and possibly on non-histone targets are likely to be of more general importance in numerous systems.

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