ases encoded by the human genome (Schofield and Ratcliffe, 2004). Other 2-oxoglutarate-dependent dioxygenases that have credible roles in cancer biology include those with long-established functions in extracellular matrix formation, such as procollagen prolyl and lysyl hydroxylases, and those with recently established functions in histone demethylation (Shi and Whetstine, 2007). Thus, it remains conceivable that HIF activation is a marker rather than the cause of oncogenic predisposition and/or that different types of tumor predisposition reflect effects on different enzyme/substrate systems. Either way, the new findings open a range of possible insights into the association of hypoxia and cancer progression.

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Modeling Synovial Sarcoma: Timing Is Everything

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Synovial sarcoma is characterized by the presence of a fusion protein involving *SYT* and *SSX2*. In this issue of *Cancer Cell*, Haldar et al. have genetically engineered a mouse model of this disease. They show that expression of the *SYT-SSX2* fusion gene yields a highly penetrant and representative model of human synovial sarcoma, but only if expression occurs in a particular biologic context. The mouse model will be a valuable resource for studying tumor biology but is also a striking example of how important understanding of normal tissue and developmental biology is to our understanding of cancer.

Sarcomas comprise a diverse group of malignant tumors of mesenchymal origin, arising in connective tissues such as fat, muscle, fibrous tissue, and bone (Helman and Meltzer, 2003). These tumors are relatively rare, with an annual incidence of seven to eight per 100,000. They account for less than 1% of all malignancies overall, but about 15% of malignancies in children. Sarcomas have historically been classified based on their site of origin, morphology, and immunohistochemical properties. Although some sarcomas can be classified easily according to these criteria and their clinical features, many present significant diagnostic challenges. However, more recently, many soft-tissue sarcomas have been shown to carry recurrent, characteristic chromosomal translocations, several of which generate fusion proteins that act as transcription factors (Table 1) (Mackall et al., 2002). As in leukemia and lymphoma, these causative genetic events provide a point of departure for sarcoma researchers. Importantly, the translocations are likely to reveal biological mechanisms whose importance transcends the rarity of these diseases. However, despite the opportunities provided by the discovery of sarcoma translocations, biological understanding of many sarcomas remains limited. The rarity of sarcomas and their clinical heterogeneity, even within a single histologic classification, present the greatest obstacles.

Table 1. Chromosomal Translocations Resulting in Fusion Genes in Sarcomas

Tumor	Translocation	Fusion Gene
Synovial sarcoma	t(X;18)(p11;q11)	*SYT-SSX* (*1*, *2*, or *4*)*
	complex rearrangements	*SS18L1-SSX1**
Ewing's sarcoma	t(11;22)(q24;q12)	*EWSR1-FLI1**
	t(21;22)(q22;q12)	*EWSR1-ERG**
	t(7;22)(p22;q12)	*EWSR1-ETV1**
	t(17;22)(q21;q12)	*EWSR1-ETV4**
	t(2;22)(q33;q12)	*EWSR1-FEV**
Clear-cell sarcoma	t(12;22)(q13;q12)	*EWSR1-ATF1**
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1**
Myxoid chondrosarcoma	t(9;22)(q22-31;q11-12)	*EWSR1-NR4A3**
	t(9;17)(q22;q11.2)	*TAF15-NR4A3**
Myxoid liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3**
	t(12;22)(q13;q12)	*EWSR1-DDIT3**
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1A**
	t(1;13)(p36;q14)	*PAX7-FOXO1A**
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*COL1A1-PDGFB*
Congenital fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Inflammatory myofibroblastic tumor	2p23 rearrangements	*TMP3-ALK*
		TMP4-ALK
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	*ASPL-TFE3**
Endometrial stromal sarcoma	t(7;17)(p15;q21)	*JAZF1-SUZ12**
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-CREB3L2**
Angiomatoid fibrous histiocytoma	t(12;22)(q13;q12)	*EWSR1-ATF1**
	complex rearrangements	*FUS-ATF1**

Asterisks indicate fusion genes that encode transcription factors or cofactors.

Additionally, for most sarcomas, cell line resources are also limited and, as for any cancer type, do not fully recapitulate the biology of the in vivo tumor. Animal models present a very appealing solution to several of these problems, particularly in the sarcomas that exhibit recurrent translocations. By introducing the fusion gene into an animal, one could hope to accurately model the disease process. A successful animal model could overcome many of the obstacles to the study of these rare cancers, allowing detailed investigation into the mechanism of tumorigenesis as well as providing a platform for experimental therapeutics. However, despite their histologic similarity to adult tissues, the cell of origin for many sarcomas remains ill-defined or totally unknown, significantly complicating the genetic engineering of such animal models. Furthermore, the timing and context of the expression of the fusion protein play an important role in the fusion protein's phenotypic effect. For these reasons, progressing from the discovery of a sarcoma fusion protein to construction of an animal model has proved to be challenging, though not without some success (Keller et al., 2004; Riggi et al., 2005).

Synovial sarcoma (SS) is a relatively frequent, highly aggressive sarcoma that occurs in both children and adults. It tends to arise adjacent to joints in the limbs—hence the name (the tissue that lines joints is called the synovium). However, this is a historically based misnomer; SS is not related to synovial tissue at all and is known to occur in sites far from joints, such as the thorax. SS is currently classified as a tumor of uncertain differentiation with no clear resemblance to any normal tissue. Morphologically, SS has two common subtypes, monophasic and biphasic, which are characterized by predominantly spindle cells or by a mixture of spindle cells and cells with epithelial differentiation, respectively. SS is characterized by a recurrent translocation [t(X;18)(p11;q11)] that leads to production of a fusion protein (Clark et al., 1994) (Table 1). In the vast majority of SS, the *SYT* (*SS18*) gene on chromosome 18 is fused with one of two closely related genes on chromosome X, *SSX1* or *SSX2*. The

SYT-SSX fusion differs from most sarcoma fusions in that this nuclear protein lacks a direct DNA-binding domain and appears to act as a transcriptional coregulator. Precisely how SYT-SSX transforms the normal progenitor of SS into sarcoma is unknown but is likely to depend on perturbation of normal gene expression at the chromatin level (de Bruijn et al., 2007).

In this issue of *Cancer Cell*, Haldar et al. present a mouse model of SS engineered from an *SYT-SSX2* fusion construct derived from an SS patient (Haldar et al., 2007). Through elegant use of genetic techniques, the authors produced a mouse that, with 100% penetrance, produces tumors that recapitulate many of the most important aspects of SS biology, including anatomic distribution, morphology, and gene expression. The authors capitalized on knowledge of developmental biology to target the expression of the *SYT-SSX2* fusion transcript to specific developmental stages in a particular tissue, skeletal muscle, which they posit could be the cell of origin for SS. By inserting an inactive *SYT-SSX2* fusion at the ROSA26 locus, viable mice were obtained whose progeny only express the fusion gene in crosses with Cre recombinase-expressing animals. Haldar et al. were thus able to target *SYT-SSX2* expression to specific stages of muscle development by crossing the *SYT-SSX2* mice with strains that express Cre under the control of promoters that are active at specific stages of muscle development. The success of this strategy transforms the field of synovial sarcoma research from one hampered by the progenitor cell mystery to one that could take advantage of the extensive knowledge of skeletal muscle development, one of the best understood developmental systems.

Of the muscle promoters tested, Haldar et al. demonstrate that only *Myf5-Cre* leads to the development of SS tumors. Expressing Cre under the control of an ubiquitous promoter (*Hprt*) or early muscle lineage promoters (*Pax3* or *Pax7*) results in embryonic lethality, while *Myf6* results in myopathy. The authors also suggest an interesting possibility deserving of further investigation, that the association of SS with joints may be related to specific factors in the microenvironment that promote survival of *SYT-SSX2*-expressing cells. These striking observations illustrate the critical importance of the timing of fusion transcript expression and illuminate the extent to which fusion oncoprotein action is restricted by developmental and cellular context. Only fusion protein expression under the specific developmental stage characterized by MYF5 expression leads to cancer. This is interesting both for SS, by providing evidence that human SS may derive from the myogenic lineage, and for sarcoma translocation biology in general, by establishing the remarkable specificity required for the development of a translocation-dependent sarcoma. What accounts for the great tumor specificity of translocations, which presumably occur at random in many cell types? One widely discussed possibility, now elegantly modeled in SS, is that only specific cell types are susceptible to the transforming effects of a given translocation that may reduce fitness or even cause lethality in most cell types. Further biologic insights are sure to arise from this model, which because of the high penetrance of the SS phenotype will provide a tremendous opportunities to advance SS research. Of particular interest will be the search for "second hits," genetic events that must occur in addition to *SYT-SSX2* to produce a malignant tumor. Also of general interest and quite timely are the opportunities generated by this model to explore the relation between chromatin function and cancer. Alterations of other genes that, like *SYT-SSX2*, regulate gene expression at the chromatin level are known to be associated with other solid tumors (e.g., *SMARCB1*) and leukemia (e.g., *MLL*-associated leukemias). More generally, this systematic approach to generating models might be applied to other sarcoma translocations. Refined tools for targeting translocations to specific cell populations at discrete developmental stages clearly have the potential to accomplish these difficult tasks.

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