Human synovial sarcoma is caused by a chromosome translocation, which fuses DNA encoding SSX to that encoding the SS18 protein. Kadoch and Crabtree now show that the resulting cellular transformation stems from disruption of the normal architecture and function of the human SWI/SNF (BAF) complex.

Damage to our chromosomes is an inescapable consequence of cell metabolism and division. DNA damage can take many forms, but because their repair is not always precise, double-strand DNA (dsDNA) breaks are among the most dangerous. Indeed, if a dsDNA break is repaired by nonhomologous end-joining rather than homologous recombination, it can potentially result in the fusion of DNA ends that were not supposed to be joined. Over the last couple of decades, it has become clear that chromosome breakage is not completely stochastic; certain regions are much more likely to break than others, and moreover, certain specific chromosome fusion events are also more likely than others. In some cases, chromosome translocations even fuse protein-coding genes in frame so that a specific, novel protein species arises. The existence of recurring fusion events has become clear from the study of human cancers, including several types of leukemia, and the examples of oncogenic transformations correlating with the generation of fusion proteins are unexpectedly plentiful (reviewed by Saha and Jones, 2005; Taki and Taniwaki, 2006). Interestingly, in the last couple of decades research has shown that the transforming fusions are often between a protein with a general function in transcription or in chromatin modification and a “targeting domain” in another protein (a DNA-binding domain, for example). It is easy to imagine how such protein fusions might lead to cellular deregulation: genes in the vicinity of the recognition sites for the DNA targeting domain could be inappropriately activated (or, alternatively, repressed), resulting in cellular transformation. A much studied example is the fusion of the DNA-binding domain of MLL to subunits of the so-called super elongation complex (Smith et al., 2011). As with mixed-lineage and acute myeloid leukemias (MLL and AML, respectively), human synovial sarcomas are caused by translocations generating new fusion proteins. The translocation event observed in this type of cancer fuses the SS18 gene on chromosome 18 and one of three SSX genes (SSX1, SSX2, and SSX4) found in a cluster on chromosome X, which generates a stable SS18-SSX fusion protein (Figure 1, upper). Although earlier data suggested that SS18 interacts with chromatin-remodeling complexes (Thaete et al., 1999; Nagai et al., 2001), the molecular consequence of fusion protein expression have been unclear.

In a detailed and compelling study published in this issue of Cell, the mechanism of cellular transformation in human synovial sarcoma is now unveiled. Kadoch and Crabtree (2013) initially provide evidence that SS18 is a hitherto overlooked, integral subunit of the human SWI/SNF (BAF) chromatin-remodeling complex. However, their detailed analysis now shows that fusion of SS18 to the SSX proteins in synovial sarcoma results in the incorporation of SS18 into the multisubunit BAF complex, replacing the SS18 protein of normal BAF complexes. This results in eviction and degradation of the BAF47 subunit.
complex. It is tightly associated with the catalytic Brg subunit, dissociating from the multisubunit complex at a much higher urea concentration than the well-known BAF47/hSNF5/INI1 or BAF250/ARID1 subunits, for example. Importantly, the SS18-SSX fusion protein becomes incorporated into the BAF complex in place of SS18, and this in turn results in the eviction, and subsequently proteasomal degradation, of the BAF47 subunit (Figure 1, lower).

BAF47 is already a well-established tumor suppressor. For example, loss of the BAF47 gene causes extremely aggressive malignant rhabdoid tumors (MRTs), and its re-expression in MRT cells stops their proliferation (Kia et al., 2008). It might therefore be expected that eviction of BAF47 also plays an important role in human synovial sarcoma tumorigenesis. In agreement with this idea, the altered BAF complex binds the Sox2 locus and reverses polycomb-mediated repression, resulting in activation of this pluripotency gene. Sox2 is uniformly expressed in human synovial sarcoma tumors and is essential for their proliferation, so its anomalous activation may well be transformative.

It is intriguing that eviction of BAF47, and thus transformation, depends on only two amino acids of the SSX protein, explaining why SSX1, SSX2, and SSX4, but not SSX3, are observed in synovial sarcoma fusion proteins: SSX3 has methionine-isoleucine in place of the evicting lysine-arginine amino acid pair found in the otherwise highly conserved SSX homologs. Altogether, this fascinating story of a unique oncogenic transformation mechanism underscores the frustratingly random nature of human cancer: if it invariably elicits efficient programs to drive cellular transformation, even an exceedingly rare and unlikely event like that in human synovial sarcoma may become a recurring human health issue.

Encouragingly, the findings of Kadoch and Crabtree indicate potential avenues of therapeutic intervention. As the authors point out, if—for example—a decoy molecule could be developed that causes the BAF47-evicting amino acids of the transformative SSX molecules to resemble the corresponding surface of the benign SSX3 protein it would offer some hope for the development of a new treatment that builds on understanding the fusion protein’s unusual mechanism of action.

REFERENCES

Ring around the Ro-sie: RNA-Mediated Alterations of PNPass Activity

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Chen et al. demonstrate a new way by which noncoding RNAs tailor the function of multicomponent complexes. They show that a noncoding RNA interacts with an exoribonuclease, altering its substrate specificity and enzymatic activity by serving as a ribonucleoprotein scaffold and, perhaps, a gate for entry of the RNA substrate.

Multiprotein complexes are the workhorses of the cell and provide critical functions that are necessary for cellular growth and viability by merging related activities into compact molecular machines. Protein-protein interactions are well known to be involved in allosteric regulation, altering substrate specificity and localization of enzymatic function to specific subcellular compartments. Several RNAs that serve as scaffolds for such molecular machines have been described, including yeast TLC1 RNA and telomerase (Lebo and Zappulla, 2012), pRNA and the O29 DNA-packaging motor (Harjes et al., 2012), and IRES elements and translation factors. The ability of RNAs to scaffold molecular machines is also being investigated for synthetic biology applications (Delebecque et al., 2012). Given the