Genomics

Major finding: L1 retrotransposition–mediated 3′ transductions occur in approximately 25% of cancer genomes.

Concept: Individual L1 source element activity is heterogeneous and fluctuates during tumor evolution.

Impact: Dispersion of nonrepetitive DNA via 3′ transductions may contribute to the mutational landscape of tumors.

L1 RETROTRANSPOSITION TRANSDUCES NONREPETITIVE DNA THROUGHOUT CANCER GENOMES

Long interspersed nuclear element 1 (L1) retrotransposons are abundant repetitive DNA elements that hijack the cellular transcription and translation machinery to copy and reinsert themselves across the human genome. Mobilization of L1 elements in the germline contributes greatly to genetic diversity, and evidence of spontaneous L1 mobilization has been observed in tumors. Neighboring nonrepetitive DNA sequences can also be mobilized during L1 retrotransposition in a process known as 3′ transduction, but whether this class of retrotransposition event is prevalent in human cancer genomes is unclear. Tubio, Li, Ju, and colleagues developed a bioinformatic pipeline to detect somatic L1 retrotransposition events in 12 different cancer types using whole-genome sequencing data from matched tumor and normal samples of 244 patients. At least one somatic L1 retrotransposition event was found in 53% of patients, most frequently those with colon cancer or lung cancer. Overall, 3′ transductions were identified in 25% of patients, and accounted for 24% of all somatic L1 retrotransposition events detected. The activity of individual L1 elements was heterogeneous, with the vast majority of 3′ transductions originating from relatively few L1 loci. L1 element activity also varied between cancer types and fluctuated during evolution of individual tumors, and was correlated with L1 promoter hypomethylation. Somatic retrotranspositions preferentially inserted into intergenic or heterochromatic regions, but coding regions were sometimes captured by somatic 3′ transductions, with proximal exons or entire genes mobilized to different genomic loci as a result of 2.3% of L1 retrotransposition events, as were putative regulatory regions, with DNase I hypersensitive sites and transcription factor binding motifs copied and inserted elsewhere in the genome by 6.6% and 13.1% of L1 retrotransposition events, respectively. Although larger, integrative studies are needed to assess the functional consequences of 3′ transduction during tumorigenesis, these findings indicate that this type of somatic retrotransposition contributes significantly to structural variation in cancer genomes. ■

Tubio JM, Li Y, Ju YS, Martincorena I, Cooke SL, Tojo M, et al. Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes. Science 2014;345:1251343.

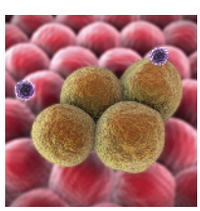
Tumor Microenvironment

Major finding: HSF1-mediated transcriptional programs in CAFs support a pro-oncogenic state in cancer cells.

Mechanism: Stromal HSF1 promotes tumor cell growth in part via activation of TGFβ and SDF1 signaling.

Impact: HSF1 is a potential therapeutic target that may enable inhibition of both cancer and stromal cells.

STROMAL HSF1 SUPPORTS TUMOR PROGRESSION IN A NON–CELL-AUTONOMOUS MANNER



It is well-established that cancer cells rely on non–cell-autonomous signals from cells within the surrounding microenvironment, including cancer-associated fibroblasts (CAF), for growth and survival. However, the transcriptional regulators that mediate reprogramming of these stromal cells to support tumorigenesis remain unknown. Activation of the transcriptional regulator heat shock factor 1 (HSF1) in cancer cells has been shown to promote tumor progression, prompting Scherz-Shouval and colleagues to explore an additional role for HSF1 in the tumor stroma. Patient-derived samples of various tumor types exhibited activation of HSF1 in CAFs in the tumor-associated stroma. Depletion of *Hsf1* in mouse embryonic fibroblasts (MEF) reduced tumor growth in xenograft breast cancer models and resulted in a less malignant tumor morphology, suggestive of a protumorigenic role for HSF1 activation in CAFs. Coculture studies supported these *in vivo* data in multiple breast cancer cell lines, and gene expression analyses revealed that stromal HSF1 regulated transcriptional programs in both cancer cells and fibroblasts that enhanced the malignant potential of cancer cells in a non–cell-autonomous manner. Of note, the HSF1-dependent gene signature in fibroblasts was distinct from the program induced by HSF1 activation in cancer cells and from the heat-shock response. The primary molecular mediators of this HSF1-driven phenotype were identified as TGFβ and stromal-derived factor 1 (SDF1), which were both upregulated in MEFs in an HSF1-dependent manner; depletion or inhibition of these proteins in MEFs inhibited the growth of cocultured cancer cells. Furthermore, in both early-stage breast and lung cancer, high stromal HSF1 expression was correlated with decreased disease-free and overall survival. These findings establish HSF1 as a critical mediator of transcriptional reprogramming in stromal fibroblasts that supports tumor growth. Moreover, these data highlight HSF1 inhibition as a therapeutic strategy to simultaneously target both cancer cells and the protumorigenic stroma in advanced cancers. ■

Scherz-Shouval R, Santagata S, Mendillo ML, Sholl LM, Ben-Aharon I, Beck AH, et al. The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. Cell 2014;158:564–78.