Telomeres

Major finding: Telomerase diffuses rapidly to find and engage telomeres in transient and stable interactions.

Approach: CRISPR/Cas9 genome editing allows for single-molecule live cell imaging to study telomerase dynamics.

Impact: Telomere dynamics suggest a model by which short telomeres may be preferentially elongated.

LIVE CELL IMAGING TRACKS THE RECRUITMENT OF TELOMERASE TO TELOMERES

Telomerase is recruited to telomeres during the S-phase of the cell cycle, where it adds repetitive DNA sequences to single-stranded 3′ overhangs of chromosome ends, preventing telomere attrition. Telomerase recruitment to telomeres involves an interaction between a component of the shelterin complex, TPP1 (also known as ACD), and the catalytic component of telomerase, TERT. However, it is unclear how telomerase finds the telomeres requiring elongation. The use of live cell imaging to understand telomerase dynamics has been limited by the low abundance of telomerase, prompting Schmidt and colleagues to use CRISPR/Cas9 to enable single-molecule live cell imaging to visualize telomerase trafficking. Genome editing generated cell lines with labeling of the endogenous *TERT* locus, telomeres, and Cajal bodies (where telomerase is predominantly localized outside of S-phase). Live cell imaging revealed that telomerase diffused quickly throughout the nucleus, excluding nucleoli, with a small proportion bound to telomeres or Cajal bodies. Telomerase formed both frequent short, dynamic interactions, and rare static, long-lasting interactions with telomeres. During the short interactions, telomerase probed chromosome ends thousands of times during a single S-phase. Both the short and static interactions required association between TPP1 and the TEN-domain of TERT. The observed dynamic telomerase–telomere interactions suggest a model in which telomerase frequently and transiently interacts with TPP1 at telomeres, only rarely forming stable interactions sufficiently long for telomere elongation, when 3′ overhangs are available for binding. This provides a potential mechanism for preferential elongation of short telomeres where telomerase would be in closer proximity to the 3′ overhang. ■

Schmidt JC, Zaug AJ, Cech TR. Live cell imaging reveals the dynamics of telomerase recruitment to telomeres. Cell 2016;166:1188–97.e9.

Melanoma

Major finding: STAG2/3 increase sensitivity to BRAF inhibition by reducing ERK activation in melanoma cells.

Mechanism: STAG2 interacts with CTCF to upregulate the ERK phosphatase DUSP6, suppressing ERK activation.

Impact: STAG2 and STAG3 suppress melanoma growth via regulation of ERK signaling.

STAG2 AND STAG3 PREVENT BRAF INHIBITOR RESISTANCE IN MELANOMA

BRAF inhibitors achieve a high response rate in patients with *BRAF*-mutant melanoma, but the majority of patients eventually acquire drug resistance. Although several resistance mechanisms have been identified, a subset of BRAF inhibitor–resistant melanomas are driven by unknown mechanisms. To discover additional resistance mechanisms, Shen and colleagues performed whole-exome sequencing of paired pretreatment and post-relapse tumor samples from a patient with BRAF inhibitor–resistant melanoma. A loss-of-function mutation in stromal antigen 2 (*STAG2*), which encodes a subunit of the cohesin complex, was greatly enriched in the post-relapse sample and was significantly mutated in The Cancer Genome Atlas pan-cancer analysis, and STAG3 loss-of-function mutations were also found in post-relapse samples. Consistent with this finding, STAG2 and STAG3 expression were reduced in BRAF inhibitor–resistant melanoma cell lines and in 7 of 9 post-relapse samples from patients with melanoma treated with BRAF inhibitors alone or in combination with MEK inhibitors, suggesting that loss of STAG2/3 is involved in the development of BRAF inhibitor resistance. Depletion of STAG2 or STAG3 reduced the sensitivity of *BRAF*-mutant melanoma cells to BRAF inhibition *in vitro* and *in vivo* via reactivation of MAPK signaling, as evidenced by increased phospho-ERK levels. Mechanistically, depletion of STAG2 or STAG3 decreased the binding of CCCTC-binding factor (CTCF) to the promoter of the ERK phosphatase DUSP6, resulting in decreased DUSP6 expression and, consequently, enhanced ERK phosphorylation and activation. Collectively, these findings identify a previously unappreciated mechanism of resistance to BRAF inhibitors and suggest that STAG2 and STAG3 may suppress tumor growth via regulation of ERK signaling. ■

Shen CH, Kim SH, Trousil S, Frederick DT, Piris A, Yuan P, et al. Loss of cohesin complex components STAG2 or STAG3 confers resistance to BRAF inhibition in melanoma. Nat Med 2016;22:1056–61.