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Telomeres

Major finding: TZAP binds preferentially to long telomeres and promotes telomere trimming.

Mechanism: TZAP competes with the shelterin complex protein TRF2 to enable specific binding to long telomeres.

Impact: TZAP promotes telomere length homeostasis by preventing accumulation of aberrantly long telomeres.

THE TELOMERE-ASSOCIATED TZAP PROTEIN LIMITS TELOMERE LENGTH

Regulation of telomere length is essential for chromosomal stability, and short telomeres are associated with cancer and premature aging. Telomeres associate with many proteins, but the interactions have not been fully characterized. Li and colleagues found that the kruppel-like zinc finger protein ZBTB48 was associated with telomeres, and ultimately renamed it telomeric zinc finger–associated protein (TZAP). TZAP exclusively and specifically interacted with telomeres and bound directly to TTAAGGG telomeric repeats in both telomerase-positive and telomerase-negative cells. TZAP bound preferentially to long telomeres with reduced concentrations of the shelterin complex, which is enriched at short telomeres. Further, TZAP competed with the shelterin complex component telomere repeat binding factor TRF2 for telomere binding, and elevated TRF2 expression reduced TZAP binding to telomeres, providing a mechanism by which TZAP might preferentially associate with long telomeres. Overexpression of TZAP resulted in a reduction in telomere length via telomere trimming, a process in which T-loops, a secondary telomeric structure, are deleted, leading to the accumulation of extrachromosomal telomeric DNA (ECT-DNA). These findings indicate a role for TZAP in limiting telomere length. Consistent with these results, CRISPR/Cas9-mediated deletion of TZAP resulted in telomere elongation and a reduction in ECT-DNA. Taken together, these data provide a mechanism by which TZAP may preferentially bind to long telomeres to promote telomere trimming and limit telomere length, thereby preventing the accumulation of abnormally long telomeres. ■

Li JS, Miralles Fusté J, Simavorian T, Bartocci C, Tsai J, Karlseder J, et al. TZAP: A telomere-associated protein involved in telomere length control. Science 2017;355:638–41.

Clinical Trials

Major finding: Osimertinib achieved better responses than platinum–pemetrexed in patients with *EGFR*^{T790M} lung cancer.

Concept: Osimertinib extended progression-free survival in patients with central nervous system metastases.

Impact: Osimertinib may improve outcomes in patients who have progressed after first-line EGFR-TKI therapy.

OSIMERTINIB IS MORE EFFECTIVE THAN STANDARD THERAPY IN *EGFR*^{T790M} TUMORS

EGFR tyrosine kinase inhibitors (TKI) achieve high initial response rates in patients with *EGFR*-mutant advanced non–small cell lung cancer, but disease progression follows in the majority of patients, often due to the *EGFR*^{T790M} mutation that promotes resistance to first- and second-generation EGFR TKIs. Osimertinib is an oral, irreversible EGFR TKI that has demonstrated activity against EGFR^{T790M} and has shown promise in phase I and II trials for the treatment of patients with *EGFR*^{T790M} lung cancer. In an open-label phase III trial, Mok and colleagues compared the efficacy of osimertinib with platinum therapy plus pemetrexed as standard of care. A total of 419 patients with advanced *EGFR*^{T790M} non–small cell lung cancer who had progressed after first-line EGFR-TKI therapy were enrolled; 279 received osimertinib and 140 received platinum therapy plus pemetrexed. The primary endpoint was investigator-assessed progression-free survival, and secondary objectives included response rate, and safety and side-effect profiles. The median duration of progression-free survival was longer in osimertinib-treated patients, 10.1 months compared with 4.4 months for platinum–pemetrexed, and the objective response rate was 71% with osimertinib, but only 31% with platinum–pemetrexed. Osimertinib treatment also extended the duration of progression-free survival in the 144 patients with metastases to the central nervous system (CNS), 8.5 months in patients receiving osimertinib versus 4.2 months in patients receiving platinum–pemetrexed. Further, osimertinib was associated with fewer adverse events, with 23% of osimertinib-treated patients experiencing grade 3 or higher adverse events compared with 47% of platinum–pemetrexed-treated patients. Taken together, the results of this phase III trial demonstrate that osimertinib is more effective than platinum therapy plus pemetrexed in patients with *EGFR*^{T790M} lung cancer who have progressed on first-line EGFR TKIs, and indicate that osimertinib has activity even in patients with CNS metastases. ■

Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629–40.

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CANCER DISCOVERY

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