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TERT Rearrangements Identify a Subset of Aggressive Meningiomas

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Introduction

Although a significant proportion of aggressive meningiomas acquire TERT promoter (TERTp) mutations which drive TERT overexpression during progression, alternative mechanisms of telomere maintenance in meningioma are broadly unknown. TERT activating rearrangements are common in some aggressive cancers and associated with poor outcome. Therefore, we sought to assess TERT rearrangements in a large cohort of patients with progressive/high-grade meningiomas.

Methods

We determined the frequency of TERT mRNA overexpression in 126 temporally- and regionally-distinct specimens from 55 WHO grades II/III meningioma patients using reverse-transcriptase PCR. Subsequently, RNA sequencing was performed in samples with TERT overexpression to detect rearrangements. Additionally, the TERTp region was sequenced in all patients to assess hotspot mutations.

Results

We identified 9 samples from 3 patients (5%) with highly amplified TERT mRNA expression. RNA sequencing of these samples revealed a novel fusion RETREG1-TERT that was present in 2 patients, in addition to a previously-reported LPCAT1 -TERT fusion in a third case (4 samples). One of the three patients had received a course of radiation treatment prior to the emergence of detectable mRNA fusion. In all cases the TERT rearrangements began in either exon 2 or 3, upstream of the reverse transcriptase domain that begins in exon 4. In total, 10 patients (18.1%) harbored TERT alterations in our cohort: 3 TERT rearrangements and 7 TERTp mutations. Importantly, patients whose meningiomas harbored TERT alterations had a significantly worse overall survival (5.1 years, 95%CI 3.1–7.2) compared to TERT wild-type patients (18.5 years, 95%CI 14.6–22.4, $p<0.001$).

Conclusions

We discovered TERT rearrangements in a subset of aggressive meningiomas, including a novel RETREG1-TERT rearrangement. Two distinct mechanisms for TERT activation, TERT rearrangements and TERTp mutations were associated with a particularly poor outcome, suggesting a central role of telomere lengthening in the pathogenesis of aggressive meningioma. Detection of TERT alterations offers a basis for a more precise identification of patients at-risk for developing early progression of meningioma.

Learning Objectives

Understanding the mechanisms of TERT rearrangements in meningiomas.