"A Comprehensive Approach to Deciphering ALT in Human Cancers"

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Abstract: Telomere maintenance plays an essential role in the development of human cancers. Although the majority of human cancers use telomerase to stabilize their telomeres, a significant minority employ an alternative mechanism of telomere maintenance (ALT). Several lines of evidence indicate that ALT depends upon recombination, but the precise molecular basis of ALT remains undefined as do the genetic/epigenetic changes that allow cells to use this pathway. Since strategies to target telomerase are beginning to enter clinical trials, characterizing ALT will not only enhance our understanding of the contribution of telomere maintenance and DNA recombination to cancer development but will also provide crucial insights into targets suitable for therapeutic intervention in human cancers. Furthermore, as ALT is associated with a better prognosis in some cancer types, it will be important to develop tools to determine ALT status. The current methods to determine whether ALT is active in cancers are challenging and not directly applicable to clinical settings. Identification of a genetic signature of ALT will therefore have direct impact in the clinic. We propose a comprehensive strategy to identify the molecular basis of ALT that includes high throughput analysis of genetic alterations associated with ALT, a signature based loss-of-function approach to identify components of the ALT pathway, and cross-species analysis of potential candidates encompassing yeast, mice, and humans.