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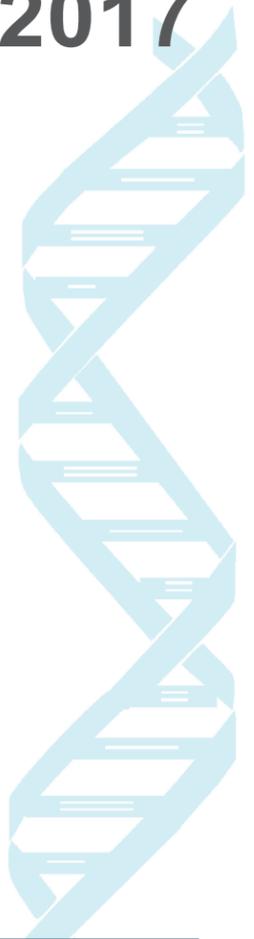
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L Laboratory Investigation

Disruption of direct 3D telomere–TRF2 interaction through two molecularly disparate mechanisms is a hallmark of primary Hodgkin and Reed–Sternberg cells

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This paper identifies two distinct mechanisms that lead to mononuclear Hodgkin cells and their progression to multinucleated Reed-Sternberg cells, the diagnostic cells of classical Hodgkin's lymphoma. Employing a unique combined quantitative 3D TRF2-telomere immune fluorescent in situ hybridization technique, Dr. Knecht revealed: a) massive attrition of telomere signals and a considerable increase of TRF2 (telomere repeat binding factor 2) signals not associated with telomeres; and b) telomere de-protection due to a loss of TRF2 signals, physically linked to telomeres.

In Western countries Epstein-Barr virus (EBV) is associated with classical Hodgkin's lymphoma in about 40% of cases. In these cases there is clear evidence that there is an association with the activation of the latent membrane protein 1 (LMP1) oncogene, which mediates chromosomal abnormalities primarily through downregulation of TRF2. The progressive breakage-bridge-fusion (BBF) cycles during the transition of a Hodgkin to a Reed-Sternberg cell result in increasing genomic instability, leading to new long BBF "zebra" chromosomes. The Reed-Sternberg cell is a cytokine secreting end-stage tumor cell that continues to recruit other precursor lymphocytes. It was surprising to discover two molecularly disparate mechanisms. It reveals that this process is more complicated than anticipated. The telomeric zinc finger-associated protein (TZAP), discovered this spring, is probably a new player in the field.