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Nuclear organization affects B-cell lymphomagenesis

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Recently we discovered a novel mechanism explaining how B-cell lymphomas might be induced during HIV infections. HIV-positive subjects have an increased risk to develop specific lymphoma subtypes including Burkitt lymphoma (BL). We recently found that viral transactivator of transcription (Tat) protein, which is released by infected cells into the blood stream, could remodel the B-cell nucleus bringing together the potential translocation partners, the MYC loci at the chromosome 8 and the IGH loci at the chromosome 14, thus increasing the probability of the t(8;14) translocation characteristic of BL. Tat induces the mobility of the MYC locus in the nucleus via induction of DSB in the vicinity of the MYC gene and its further repair by NHEJ. In order to study the mechanism of the DSB/NHEJ-induced locus relocalization, we have created and characterized the lymphoblastoid RPMI8866 cell line inducibly expressing CRISPR/Cas9 and gRNA targeting the upstream region of the MYC IGH genes. Upon induction, This leads to relocalization of the MYC locus towards the center of the nucleus and the IGH CRISPR/Cas9 generates DBDs in the target loci as well as t(8;14) translocations. Factors that increase the proximity between the MYC and IGH loci also increase the t(8;14) frequency and inversely, drugs that inhibit proximity also inhibit the translocation frequency. Therefore, we provide here the first experimental proof that spatial proximity indeed increases the probability of chromosomal translocations.

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Dysregulation of splicing factors in B-cell acute lymphoblastic leukemia

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Aberrant splicing is a hallmark of leukemias with mutations in splicing factor (SF)-encoding genes. We investigated its prevalence in pediatric B-cell acute lymphoblastic leukemias (B-ALL), where SFs are not mutated. By comparing them to normal pro-B cells, we found thousands of aberrant local splice variations (LSVs) per sample, with 279 LSVs in 241 genes present in every comparison. These genes were enriched in RNA processing pathways and encoded ~100 SFs, e.g. hnRNPA1. hnRNPA1 3'UTR was most pervasively mis-spliced, yielding the transcript subject to nonsense-mediated decay. To mimic this event, we knocked it down in B-lymphoblastoid cells and identified 213 hnRNPA1-dependent aberrant exon usage events comprising the hnRNPA1 splicing sig-