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Aberrant speckle-genome interaction facilitates oncogenic chromosomal translocations

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Chromosomal translocations play a pivotal role in the oncogenesis of various cancer types by driving the amplification of oncogenes, hijacking of enhancers, and forming fusion genes. Although it has been suggested that spatial proximity between chromosomes in interphase is a key factor of chromosomal translocations, little is known about the determinants of the spatial proximity between oncogenic genomic regions, especially for inter-chromosomal translocations. In light of recent evidence that a substantial portion of genomic regions are anchored to nuclear bodies shaping inter-chromosomal interactions, we hypothesized that aberrant regulation of nuclear body-genome interactions facilitates oncogenic chromosomal translocation by strengthening inter-chromosomal interactions. Here, by analyzing pan-cancer speckle-genome interaction from *in situ* Hi-C contact maps of 48 human cell lines, we identified genomic regions recurrently exhibiting enhanced speckle-genome interaction. These genomic regions include oncogenic fusion genes such as *BCR*, *KMT2A*, and *IGH,* showing increased inter-chromosomal interaction between fusion partners. Remarkably, reinforcement of speckle-genome interaction by MAZ overexpression in 293AD cells reproduces the enhanced inter-chromosomal interactions between fusion partners observed in cancer cells. We are further investigating whether the aberrant speckle-genome interaction facilitates oncogenic chromosomal translocation events using Cas9-based double-strand break induction upon MAZ overexpression. Taken together, our results highlight a mechanism of chromosomal translocation genesis in which aberrant speckle-genome interactions act as a bridge between oncogenic genomic regions.