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Aberrant nuclear speckle-genome interplay facilitates oncogenic chromosomal translocations

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Chromosomal translocations play a pivotal role in the oncogenesis of various cancer types. While physical interactions between loci on different chromosomes during interphase have been suggested as a key factor in chromosomal translocations, little is known about the determinants of such interactions. Here, we demonstrate that nuclear speckle-genome interactions are aberrantly regulated in cancer cells and facilitate oncogenic chromosomal translocation events by mediating interchromosomal interactions. By analyzing in situ Hi-C contact maps from 53 human cancer cell lines, we identify aberrant speckle hubs (ASHs) that recurrently exhibit enhanced nuclear speckle-genome interactions across cancer cells. Notably, recurrent gene fusions detected in patients are highly associated with ASHs and cancer cells harboring enhanced speckle interactions at ASHs show increased spatial proximity between fusion partners. We identify MAZ, a zinc finger protein that preferentially binds to ASHs, as a key driver of ASHs in cancer cells. Overexpression of MAZ significantly enhances speckle interactions at ASHs in human 293AD cells. Using CRISPR-Cas9 genome engineering, we demonstrated that MAZ-dependent speckle interactions at ASHs significantly increased the likelihood of recurrent gene fusions upon induction of double-strand breaks (DSBs). We are currently testing whether MAZ overexpression in isolated mouse pre-B cells leads to sporadic oncogenic fusion events, in order to confirm that MAZ-dependent speckle interactions at ASHs can drive the oncogenesis of B cell leukemia in vivo. Taken together, our results highlight that aberrant nuclear speckle-genome interactions induced by MAZ overexpression provide a 3D architectural background that facilitates oncogenic chromosomal translocations.