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Dissecting the unique and shared roles of MAZ and CTCF in organizing genome-speckle interactions

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Nuclear speckles are membrane-less compartments enriched in splicing and transcriptional regulators. Genomic regions positioned near speckles show elevated transcriptional output and enhanced RNA processing, emphasizing the regulatory importance of genome–speckle proximity. Despite this, the molecular mechanisms that tether the genome to speckles remain only partially understood. The transcription factor MAZ (Myc-associated zinc finger protein) has been implicated in genome–speckle association, yet its functional significance and mode of action are not fully defined. To test whether MAZ represents a unique regulator of genome–speckle association or reflects a broader property of C2H2 zinc finger proteins, we compared its function to CTCF, a canonical genome organizer also implicated in speckle-genome interplay. We assume that MAZ exerts more delayed effects on speckle association compared to CTCF. By employing HiCAN, a method to examine speckle-genome interplay using Hi-C data revealed that MAZ loss caused a marked reduction in genome–speckle proximity compared to those of CTCF depletion. Surprisingly, in our SEM (human B-ALL) dual degron system, acute depletion of canonical MAZ isoforms produced no measurable changes. This discrepancy suggests that MAZ-dependent speckle association may arise from long-term or indirect effects, or from non-canonical isoforms not targeted in our system. Genomic regions with high speckle scores exhibited shared genomic characteristics. These loci were densely co-occupied by MAZ and CTCF, and nearby genes were enriched for chromatin structure and genome organization functions, consistent with promoter-centric regulation of speckle tethering. To probe their protein complexes, we validated MAZ's association with SRRM2 by proximity ligation and are applying Split-TurboID to define the MAZ interactome enriched at speckles compared with CTCF. Taken together, these results motivate further dissection of MAZ and CTCF protein networks to determine how distinct interactomes contribute to genome–speckle organization.