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Decoding the 3D Gene Regulatory Network Driving Oncogenic MAZ Activation

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MYC-Associated Zinc finger protein (MAZ) has emerged as a critical regulator of gene expression, with roles spanning oncogene activation, transcriptional regulation, and higher-order chromatin organization. Its activity has been implicated in coordinating 3D genome architecture, processes essential for cellular identity and development. Consistent with this central role, overexpression of MAZ has been observed across a wide range of cancers, where it has been linked to altered transcriptional programs and tumor-promoting phenotypes such as increased proliferation or survival. Despite its clear oncogenic relevance, the upstream mechanisms that drive MAZ activation remain poorly understood, representing a key gap in our understanding of cancer epigenetics. To investigate the upstream regulatory circuitry, we applied an integrative approach combining high-resolution chromatin conformation capture with epigenomic profiling to map the regulatory landscape surrounding the MAZ locus. This analysis identified distal enhancer elements that physically interact with the MAZ promoter. Notably, cancer-associated members of the ZNF, KLF, and SP families emerged as key regulators acting through these MAZ-contacting enhancers. By integrating chromatin interaction data, transcription factor binding profiles, we highlight the upstream regulatory network responsible for MAZ activation. Furthermore, we aim to conduct a pooled CRISPR screen of human transcription factors to uncover regulators of MAZ overexpression. Given the dual role of MAZ in gene regulation and 3D genome organization, its overactivation may contribute to broader disruptions in nuclear architecture and transcriptional homeostasis. This work fills a critical gap in the understanding of MAZ regulation and highlights potential therapeutic targets within the enhancer-promoter interaction driving its activation.