Changes in 3D chromatin architecture upon NF-κB activation by TAX involve transcriptional and alternative splicing regulations.

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Chronic activation of NF-κB pathway contributes to HTLV-1-induced leukemogenic processes. While the effects of TAX on cytoplasmic regulation of NF-κB have been widely studied, their functional impacts at the nuclear level still remain elusive. In this context, we have recently demonstrated that, besides transcriptional regulations, nuclear import of RelA provides splice target specificity by recruiting the RNA helicase DDX17 at the vicinity of genomic exons (Ameur et al., Nat Commun 2020). This mechanism occurs independently of RelA activity on promoter, thereby raising the question whether and how RelA-mediated transcriptional and post-transcriptional processes coordinate with each other upon TAX expression.

Here, we evidenced by Chromosome Conformation Capture analysis (Hi-C) that TAX reshapes the 3D genome by inducing local changes in chromatin loops that coincide with transcriptional and alternative splicing modifications. Gene ontology analysis revealed that TAX-induced 3D chromatin looping is enriched in NF-κB responsive genes, which is consistent with recent identification of specialized NF-κB transcription factories. IF analysis also showed high enrichment of DDX17 in TAX speckles. Using 4C and 3C assays, we evidenced that, while undergoing no transcriptional modifications, RelA/DDX17 splicing target genes physically interact with genes transcriptionally deregulated by TAX. For instance, gene interactions between *NFKBIA* and *RELA* coincided with enriched RelA occupancy of both the *NFKBIA* promoter and the genomic exon 6 of *RELA* (but not at its promoter) that corresponded to an increase in *NFKBIA* expression and the skipping of exon 6 from the *RELA* transcript. Using dCas9 constructs able to affect gene interactions and/or their functional regulation, we demonstrated a causal relationship between gene-gene contacts and alternative splicing regulation by RelA and DDX17 upon TAX. These data describe a new mechanism that links transcriptional and post-transcriptional perturbations induced by TAX-mediated NF-κB activation to dynamic changes in the 3D conformation of the host cell genome.

Disclosure of Interest Statement:
None