Quantifying the Temporal Dynamics between Genome Folding and UV-induced DNA Damage Response

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Chromosome conformation has been typically linked to transcription and replication, which has been the focus of many studies. However, recognizing the extremely dynamic activity of chromatin contacts has shifted the emphasis of study in recent years toward its coupling in creating adaptive repair networks. Studies have been conducted to learn how the genome is protected from double-stranded breaks and different types of damage sources[1, 2], but considerably less has been done for cancer-causing bulky DNA lesions, which are generally introduced by UV damage and repaired by nucleotide-excision repair (NER).

Using Hi-C contact maps we derived from UV-irradiated HeLa cells with 12, 30, and 60 minute recovery durations, we investigated 3D genome folding and its relation to NER activity. We examined the various hierarchical 3D genome architecture layers, including TADs, that change dynamically in response to UV damage. Under matching experimental conditions, we also generated RNA-seq samples. In addition, we provide a novel method for understanding the differential chromatin contacts for mutual comparison of two Hi-C contact maps with an emphasis on short-range interactions. We employ a Graph Neural Network (GNN) model to detect whether sub-interactions of a graph created from one Hi-C matrix are also retained in the other. Using this technique, we quantify the magnitude of differential change around each bin along the diagonal of an equally divided Hi-C contact map and decide whether a genomic region is differential. As part of this multi-omics strategy, we obtained Damage-seq[3] and XR-seq[4] samples to show NER activity in the specific genomic areas identified by differential time course analysis.

Our work establishes evidence for the notable effects of UV-irradiation on 3D structure and genome integrity, and offers a model in which, when exposed to UV light, differential chromatin compaction is associated with dramatically elevated repair rates.

References

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