Unraveling the Role of 3D Genome Organization in Modulating DNA Damage Susceptibility and Gene Expression during Chemotherapy

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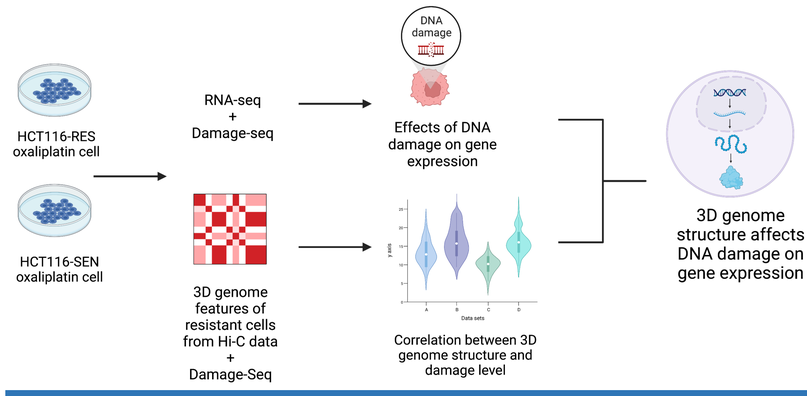
Abstract

Platinum-based chemotherapy drugs kill cancer cells by damaging DNA. Previous studies have found that the 3D genome structure of cells can influence the distribution of chemotherapy-induced DNA damage. However, the explicit role this regulation plays in drug resistance remains unexplained. Our research explores the relationship between alterations in 3D genome structure of cancer cells and their resistance to platinum-based chemotherapy. By comparing oxaliplatin-resistant and sensitive cells, we observed that changes in DNA damage levels across genomic regions correlate with their nuclear location. Genomic regions near the nuclear speckle displayed reduced damage levels in resistant cells, suggesting that 3D genome adaptations increase resistant cell survival. Additionally, we identified genes with high speckle association frequency that exhibited reduced damage and increased expression levels, implicating them in platinum-drug resistance. This study contributes to our understanding of the interplay between 3D genome structure and chemotherapy resistance, offering potential new avenues for cancer treatment strategies.

Background

- Platinum derivatives such as cisplatin and oxaliplatin are classic chemotherapy drugs, where DNA is the primary cellular target.
- The resistance to platinum-based drugs can be either intrinsic, existing within cells before treatment, or can be developed as the result of treatment itself.
- Sub-nuclear cellular architecture has been shown to play a role in the exposure of certain genomic regions to concentrations of cisplatin, leading to higher cisplatin-induced damage.
- Differences in platinum drug induced DNA damage distributions could then lead to differences in overall gene expression levels.
- No current studies have explored the relationship between nuclear locations of genomic regions and their vulnerability to oxaliplatin-based chemotherapy drugs.

Methods



References

Wang, Y., et al. (2023) The 3D genome organization plays a key role in chemotherapy-induced DNA damage susceptibility [Manuscript in preparation].

Rottenberg, S., Disler, C. and Perego, P. (2021) The rediscovery of platinum-based cancer therapy. Nat Rev Cancer, 21, 37-50.

Methods figure created with BioRender.com

Results

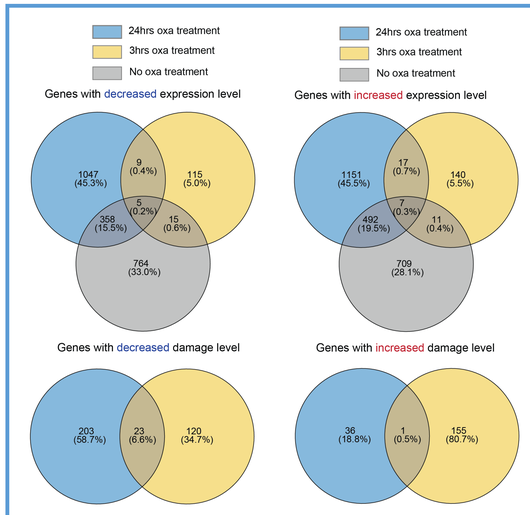


Figure 1: Counts of significant shared and unique genes between resistant and sensitive cells after 3hrs, 24hrs, and no oxaliplatin treatment.

- More genes show significant gene expression in the 24hr and control groups, including a substantial number of shared genes between 24hr and control.
- Resistant cells return to a state resembling the control cell after 24 hours of treatment.
- Fewer 24hr genes show increased damage than decreased damage.
- Highly damaged genes are likely repaired at some point between 3hrs and 24hrs of treatment.

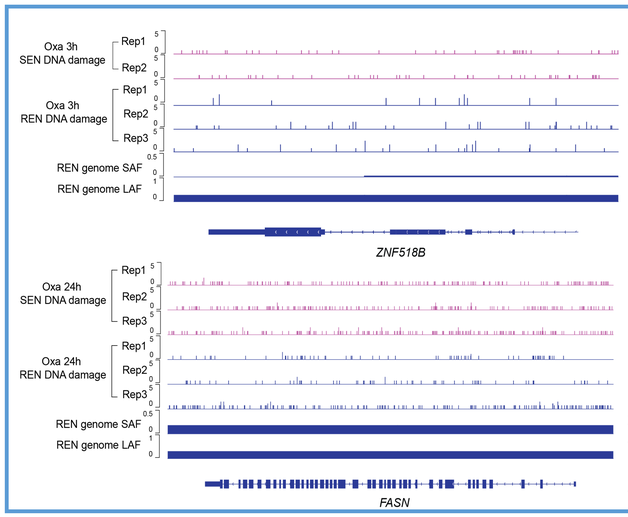


Figure 2: Comparison of damage sites between resistant and sensitive cells for specific genes.

- *ZNF518B gene*
  - 3hrs specific
  - Down damage
  - Down regulated
  - Low SAF
  - Low LAF
- *FASN gene*
  - 24hrs specific
  - Down damage
  - Up regulated
  - High SAF
  - Low LAF

SAF: speckle association frequency
LAF: lamina association frequency

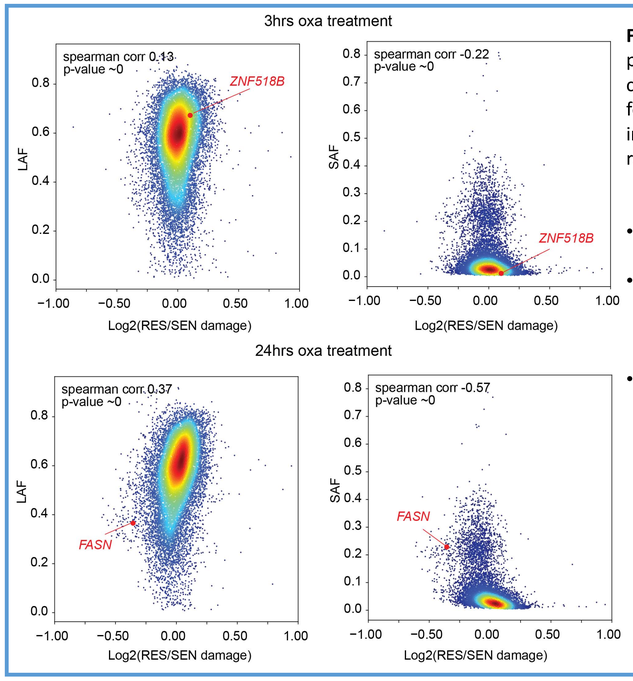


Figure 3: Correlation plot of damage fold change vs. Structural features, plotted by individual genomic regions.

- Correlation strength increases over time
- High damage regions more likely to be near nuclear lamina.
- Low damage regions more likely to be near nuclear speckle.

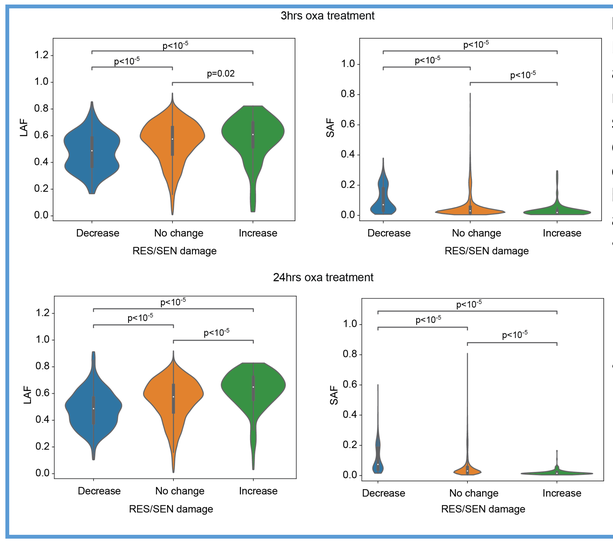


Figure 4: Nuclear Lamina/Speckle association frequency for cells showing increased, decreased, or no change in damage between resistant and sensitive cells.

- High damage regions in resistant cells closer to the nuclear lamina.
- Low damage regions in resistant cells closer to nuclear speckles.

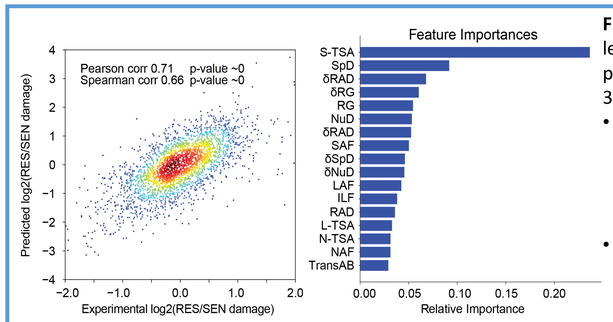


Figure 5: Machine learning model to predict damage with 3D genome features

- High correlation between predicted and actual damage fold change (in 24hr sample)
- Speckle related features are most important for prediction

Discussion

We originally hypothesized that the 3D genome structure in colorectal cancer cells influences the vulnerability of a genomic region to DNA damage induced by platinum drug. The findings of the project support the validity of these hypotheses. Below are some conclusions derived from our findings:

- Varied levels of oxaliplatin-induced damage across the genome are observed between the resistant and sensitive colon cancer cell lines.
- The varying genome-wide levels of oxaliplatin damage observed in genes from resistant and sensitive colon cancer cell lines are associated with differences in 3D genome positioning.
- Differences in transcriptome profiles are shown when comparing genes from resistant and sensitive colon cancer cell lines. Some genes were involved directly in platinum resistance, and these genes have varied DNA damage level and distinct 3D structural features.

These results allow for a deeper understanding of oxaliplatin function and further advance the study of drug resistance in cancer cells.

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