Weill Cornell Medicine

Single-Cell Platform for Mapping DNA Damage in Disease and Aging

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Background & Unmet Need

- DNA damage is a critical factor in cellular aging and disease, but current technologies can only measure damage across bulk cell populations
- Single-cell approaches have revolutionized our understanding of cell-specific molecular programs but mapping DNA damage at single-cell level has remained challenging
- The stochastic nature of DNA damage formation complicates investigation of its relationship with other cellular functions
- **Unmet Need:** Methods that can simultaneously map DNA damage and gene expression at single-cell resolution to understand how DNA damage impacts cellular function

Technology Overview

- **The Technology:** A high-throughput method, termed Paired-Damage-seq, that enables simultaneous mapping of oxidative & ssDNA damage with transcriptomes at single-cell resolution
- The "labeling-by-repair" approach uses DNA repair proteins to remove existing DNA damage sites, followed by incorporation of biotin-modified dUTPs at the damaged sites
- The method combines Paired-Tag RNA sequencing with split-pool barcoding to enable high-throughput analysis of hundreds of thousands to million of cells
- **PoC Data:** Validated in HeLa cells with strong agreement to existing bulk methods, showing 87% correspondence with RNA-seq and 72% similarity to CLAPS-seq DNA damage profiles
- Successfully applied to mouse brain tissue demonstrating cell-type specific damage patterns
- Demonstrated connection between DNA damage accumulation and epigenetic information loss

Inventors:
Chenxu Zhu
Dongsheng Bai

Patents:
Provisional Filed

Publications:
Bai et al. *Nat Methods*. 2025.

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Technology Applications

- Screen chemical compounds to identify promising drug candidates
- Identify and validate therapeutic targets to develop cell-specific treatments based on DNA damage patterns
- Facilitate biomarker discovery for diseases associated with DNA damage and repair deficiencies

Technology Advantages

- Simultaneously measures DNA damage and gene expression at single-cell resolution
- High-throughput capability at single-cell resolution
- Seamless integration with existing sequencing workflows and screening platforms

Supporting Data / Figures

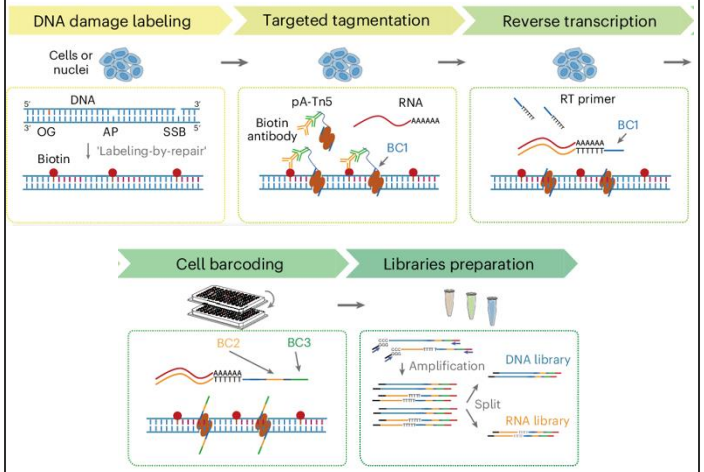

Figure 1: Schematic of the Paired-Damage-seq workflow with the 'Labeling-by-repair' strategy to label damage sites. OG, 8-oxoguanine; AP, apyrimidinic site; RT, reverse transcription.

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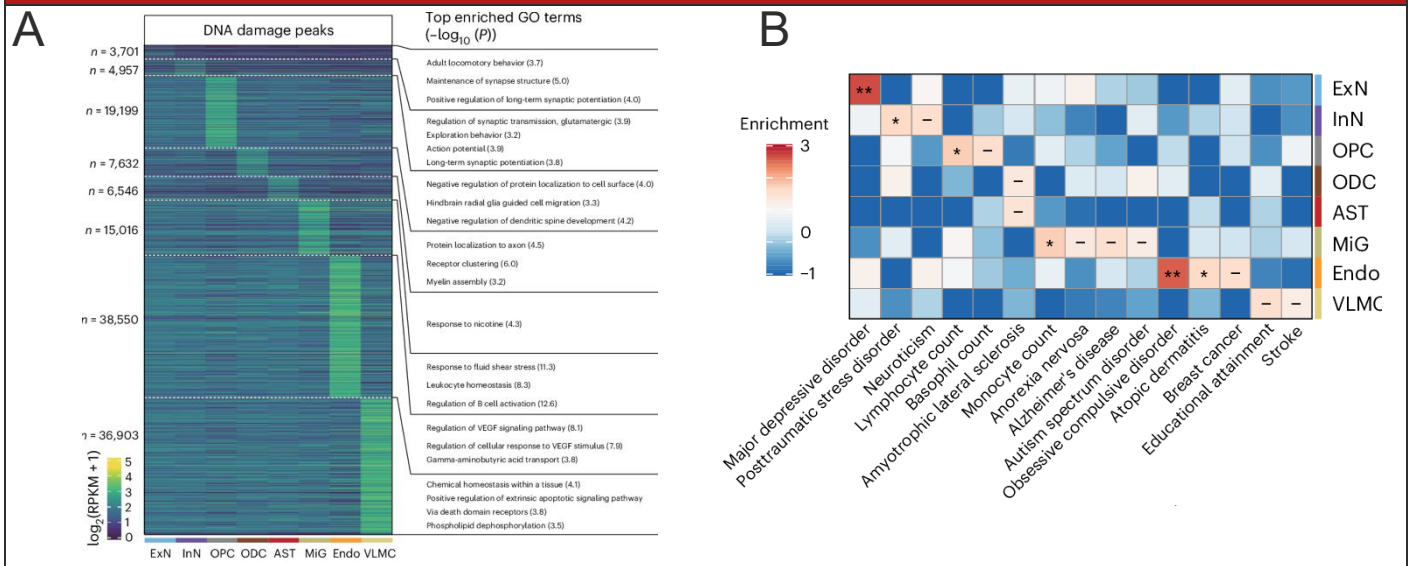

Figure 2: A) Heatmap of cell-type-specific DNA damage peaks across different cell types (ExN, InN, OPC, ODC, AST, MiG, Endo, VLMC). Each cell type has distinct GO terms associated with its damage patterns, reflecting their specific biological functions. B) Heatmap showing associations between DNA damage peaks and various diseases/traits from GWAS studies.

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