Global Congress on Public Health 2025

July 23-24, 2025 | Paris, France

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Thiopurine-Induced Mutagenesis at Methylated CpG Sites Drives TP53 R248Q Hotspot Mutations in Relapsed ALL

Background

Acute lymphoblastic leukemia (ALL), the most common childhood hematological malignancy, faces a critical challenge of chemoresistance driven by therapy-induced genomic instability. Thiopurines, cornerstone drugs in ALL maintenance therapy, promote this instability and relapse-associated mutations, especially in mismatch repair-deficient (dMMR) patients. Notably, TP53 hotspot mutations like R248Q are significantly enriched at relapse. However, the molecular mechanisms driving this specific enrichment during thiopurine treatment, particularly at methylated CpG sites, remain unclear.

Objective

This study aims to elucidate the mechanism underlying the enrichment of TP53 R248Q hotspot mutations in ALL relapse and to explore potential intervention strategies.

Result

Acute lymphoblastic leukemia (ALL) relapse is frequently driven by chemoresistance mutations. To clarify the basis of TP53 R248Q enrichment, we first confirmed its significant overrepresentation at relapse (4.5% at diagnosis vs. 21.2% at relapse, P=0.005). To identify the mutational processes driving this enrichment, multi-omics analysis of relapsed ALL cohorts revealed that thiopurine treatment synergizes with dMMR to generate a distinct mutational signature (thio-dMMR), characterized by preferential C>T mutations at methylated CpG sites—aligning with the methylated CpG focus in the background. To directly test whether DNA methylation contributes to this CpG-specific mutagenesis. Functional experiments demonstrated that: DNA methylation critically regulates mutagenesis: 5-Methylcytosine (5mC) at CpG sites promotes thiopurine-induced C>T mutations. Targeted demethylation or DNMT inhibition (e.g., Decitabine/DAC) significantly suppresses mutation burden ($P<2.2\times10^{-16}$ for methylated vs. unmethylated CpG sites).

Therapeutic intervention

Given that methylation drives mutagenesis, combining DAC with thiopurine reduces CpG methylation and inhibits the acquisition of R248Q-mediated multidrug resistance, providing a strategy to prevent relapse evolution.

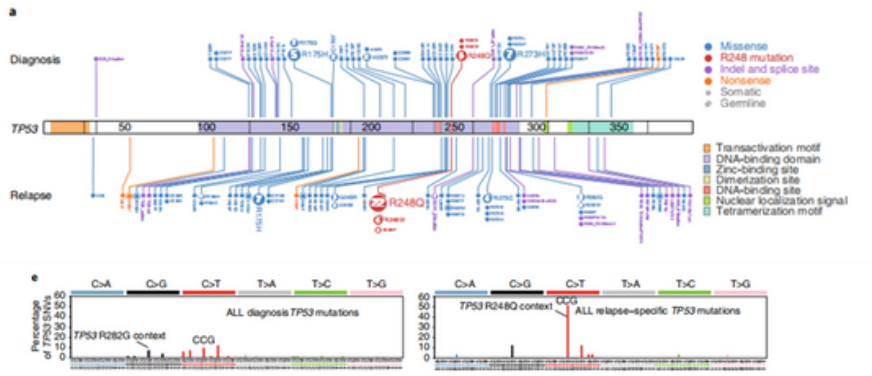
Conclusion

This methylation-dependent mutagenesis mechanism elucidates the genomic basis of TP53 hotspot mutations in relapsed ALL and offers actionable targets to overcome therapy-induced resistance.

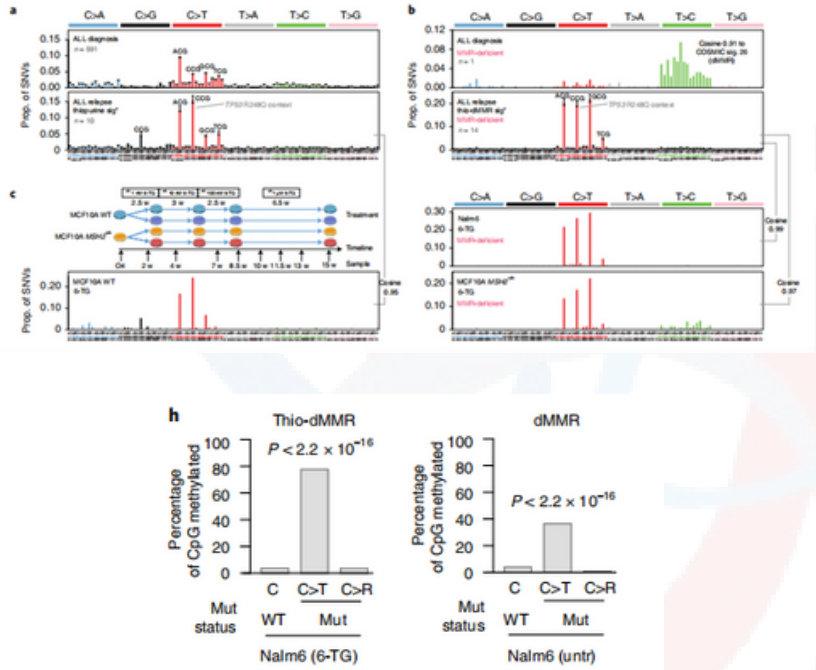
ISBN: 978-1-917892-10-0

doi.org/10.51219/URForum.2025.Xiaomeng-Li

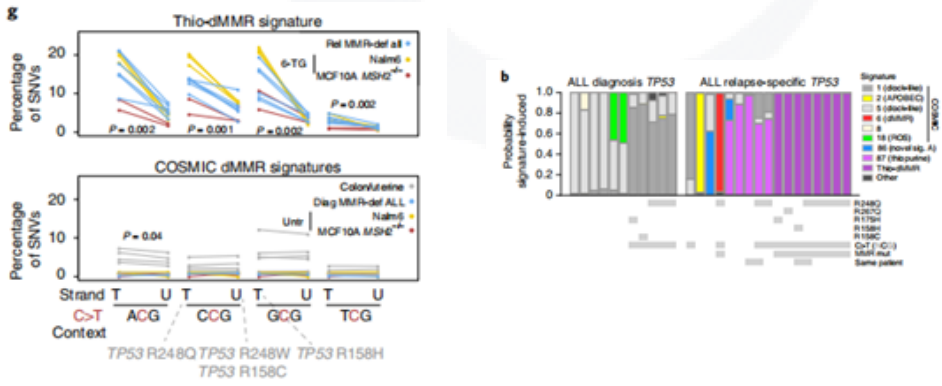
1. 强调TP53 R248Q在复发ALL中的富集（Fig 1a,e）



2. Thio-dMMR特征驱动甲基化CpG位点的C>T突变



3. DNA甲基化调控诱变：5mC促进突变，DAC抑制突变负担(2g,3h)



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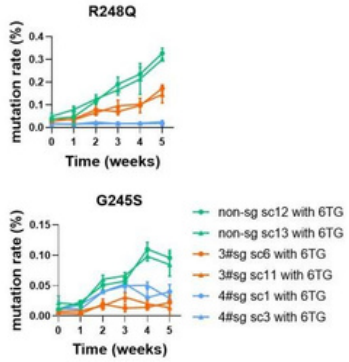
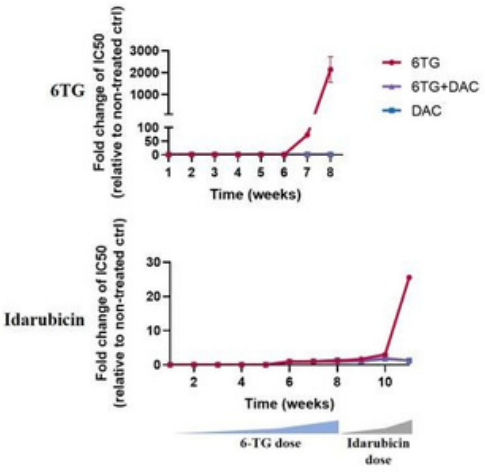
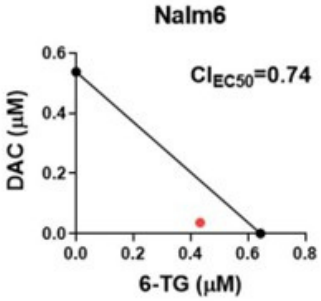
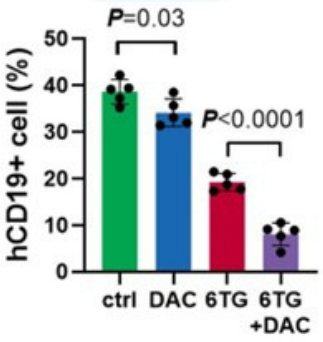


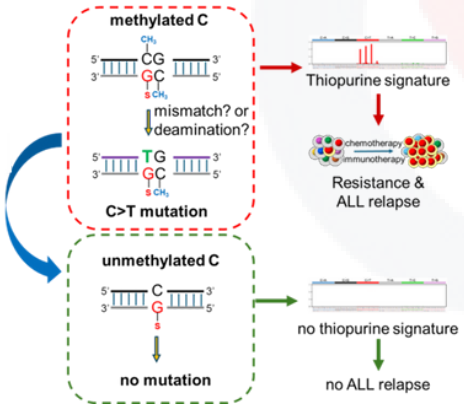
4. Therapeutic intervention







5. Conclusion



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