38th World Congress on
Pharmacology

June 23, 2025
Webinar

Xiaomeng Li, J Clin Exp Pharmacol 2025, Volume 15

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Thiopurine-induced mutagenesis at methylated CpG site drives multiple relapses in ALL clonal evolution

Acute lymphoblastic leukemia (ALL) is the most common blood cancer in children. A key challenge in its treatment is resistance to chemotherapy, particularly to mercaptopurine, a drug used in maintenance therapy. Recent research has uncovered that mercaptopurine can induce specific C>T mutations at CpG sites in patients with defective mismatch repair (dMMR), a pattern known as the thio-dMMR signature. These mutations are driven by DNA methylation, specifically 5-methylcytosine (5mC). Reducing methylation—either by removing 5mC at specific sites, knocking out DNA methyltransferase genes, or using the demethylating agent decitabine (DAC)—significantly decreases these mutations. Combining DAC with mercaptopurine not only lowers CpG methylation but also reduces mutations in drug resistance–related genes like NR3C1 and NT5C2, thereby preventing the development of drug-resistant leukemia cells. This study is the first to demonstrate that DNA methylation directlyinfluences mercaptopurine-induced mutations through a 5mC-dependent mechanism. The findings suggest that targeting DNA methylation could be a promising strategy to prevent chemoresistance and relapse in ALL, offering a new direction for epigenetic intervention in cancer therapy.

Biography

Dr. Xiaomeng Li, a Ph.D. candidate in Oncology at Shanghai Jiao Tong University School of Medicine, focuses on the molecular mechanisms of chemotherapy resistance in leukemia. With multiple high-impact publications in Leukemia and Nature Cancer, her research explores DNA methylation and mismatch repair deficiencies. She has received numerous academic honors and actively participated in national research projects, demonstrating strong scientific rigor and innovation.

Received: April 03, 2025; **Accepted**: April 06, 2025; **Published**: July15, 2025