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COMMENTARY

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Diabetes drug crosses over: Metformin emerges as novel therapeutic option for hematologic malignancies

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At the physical level, time is the ultimate equalizer, generously granting every individual twenty-four hours daily. Biologically, however, time operates unfairly by imposing age-related biological consequences. Hematopoietic stem cells (HSCs) tirelessly generate new blood cells throughout our lives, yet their continuous self-renewal and replication accumulate mutations over time. Certain mutations confer selective proliferative advantage to HSCs, termed clonal hematopoiesis (CH). CH represents a mutation-driven aberrant expansion of blood cells. Mounting evidence reveals that CH intensifies with aging, earning its designation as "age-related CH". CH demonstrates strong associations with hematologic malignancies such as acute myeloid leukemia (AML), cardiovascular disease, myocardial infarction, chronic obstructive pulmonary disease, and Alzheimer's disease. Notably, individuals with CH exhibit a 10-fold elevated leukemia risk compared to the general population.

GENETIC DRIVERS AND MUTATIONAL SPECIFICITY

DNMT3A, TET2, and ASXL1 mutations are the primary drivers of CH. DNMT3A mutations, prevalent in AML, exhibit age-dependent clinical significance. As the most frequently mutated gene in CH, DNMT3A encodes a DNA methyltransferase that carries out *de novo* DNA methylation. Germline mutations in DNMT3A are associated with Tatton-Brown-Rahman syndrome, characterized by symptoms such as excessive height, intellectual disability,

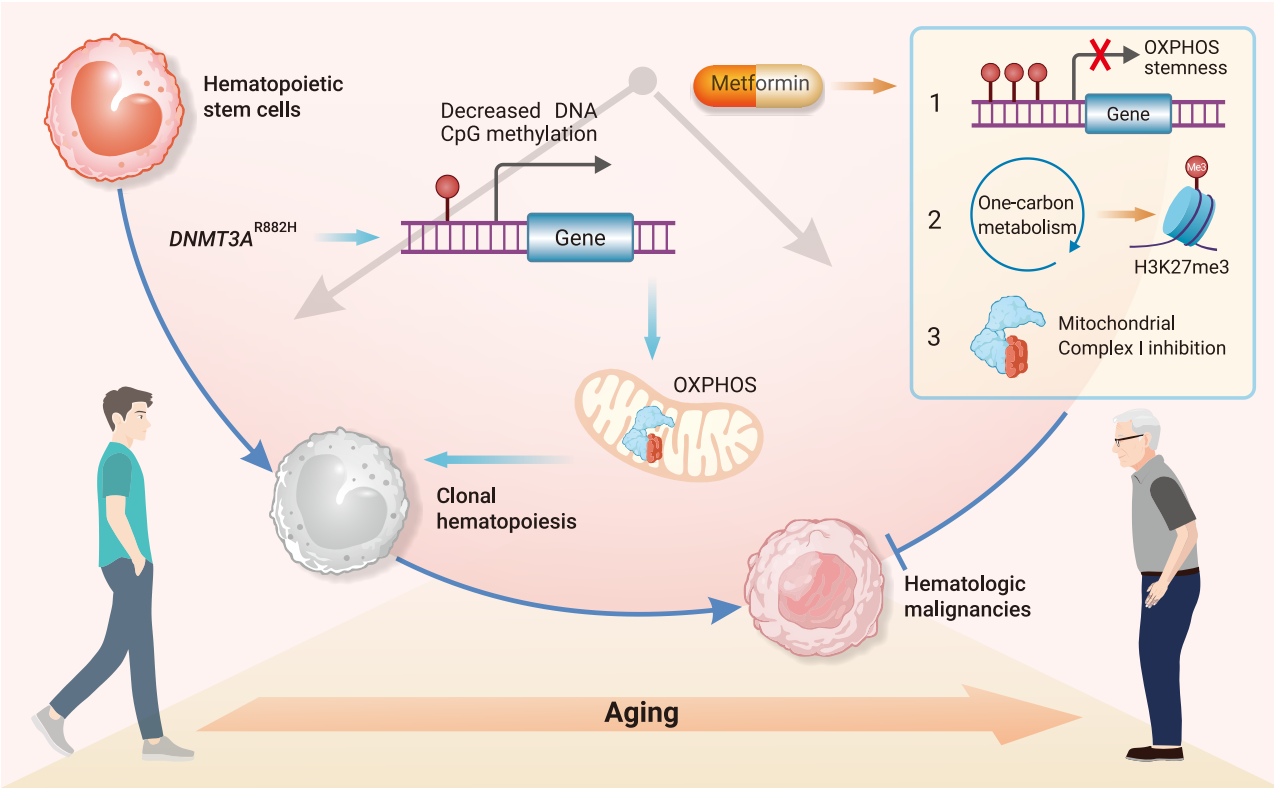

Figure 1. Mechanism of DNMT3A mutation-promoted clonal hematopoiesis and hematologic diseases, and metformin intervention strategy With aging, the mutation rate of genes in hematopoietic stem cells (HSCs) increases. The *DNMT3A*^{R882} mutation reduces the methylation levels of DNA CpG islands, thereby promoting the expression of stemness-related genes and mitochondrial oxidative phosphorylation (OXPHOS) genes. This endows mutant HSCs with sustained proliferative advantages (termed clonal hematopoiesis (CH)) and oncogenic capabilities. Notably, metformin, a first-line drug for type 2 diabetes treatment, inhibits DNMT3A mutation-driven CH and acute myeloid leukemia (AML) progression mainly through three mechanisms: 1) enhancing DNMT3A methyltransferase activity to promote DNA promoter methylation, thereby suppressing the expression of stemness and OXPHOS genes; 2) up-regulating one-carbon metabolism genes and metabolites to increase H3K27me3 levels, reshaping the epigenetic landscape of mutant cells; 3) based on its classic function of targeting mitochondrial complex I to inhibit energy production.

and obesity, while somatic mutations dominate aging-related hematopoietic malignancies. In 2010, Ley *et al.* first reported the correlation between somatic mutations of DNMT3A and AML in the *New England Journal of Medicine*, and identified that R882 hotspot mutation in DNMT3A is common in CH and associated with increased risks of myeloid malignancies. While *DNMT3A*^{R882} mutations are correlated with poor prognosis in elderly patients, non-R882 DNMT3A variants predict adverse outcomes in younger cohorts. The mechanisms by which these mutations have strong mutagenic and

proliferative effects in HSCs remain elusive. The clinical intervention strategies are still limited.

PRECLINICAL DISCOVERY OF DNMT3A-MUTANT CH

To address these questions mentioned above, by analyzing public RNA-seq and scRNA-seq datasets, Dr. Steven M. Chan's group at Princess Margaret Cancer Centre reveals the significantly elevated levels of oxidative phosphorylation (OXPHOS) and up-regulated related genes such as Ndufv1 and Cox15 in *Dnmt3a*$^{R878H/+}$ mice (analogous to human *DNMT3A*$^{R882H/+}$ mutations) compared to wild-type controls (Figure 1).[1] Independently, Dr. George Vassiliou's group at University of Cambridge also established a conditional *Dnmt3a*$^{R882H/+}$ mouse model mimicking human R882 mutations. The lifespan of *Dnmt3a*$^{R882H/+}$ mice is significantly shortened, accompanied by an increased incidence of myeloproliferative neoplasms and AML. Using whole-genome CRISPR screening, they identify the dysregulated mitochondrial metabolism-associated genes including Slc25a1, Ndufb11, Pdhb, and Cs, in *Dnmt3a*$^{R882H/+}$ hematopoietic stem and progenitor cells (HSPCs) (Figure 1).[2] Analysis of the RNA sequencing data of patients with primary AML reveals that the expression of OXPHOS genes in patients with *DNMT3A*^{R882} mutation is increased compared with that in control group.

METFORMIN: CROSSTALK WITH EPIGENETIC MODIFICATION

Both teams found that metformin, a clinically approved oral antidiabetic agent targeting mitochondrial complex I, with clinically relevant concentrations (50 μM) significantly suppress R882 mutation-driven clonal expansion and proliferative advantage by targeting OXPHOS-related genes and metabolic pathways up-regulated in mutant cells, while having no significant effect on non-mutant cells. Steven M. Chan's group further analyzed metabolites and genes vital for energy and redox metabolism, and found that metabolites linked to one-carbon metabolism, including L-cysteate, dimethylglycine, reduced glutathione (GSH), and taurine are increased after metformin treatment. Consistently, genes encoding enzymes for folate and methionine metabolism were up-regulated in mutant cells with metformin treatment. Since one-carbon metabolism is known to regulate DNA and histone methylation, further multi-omics analysis revealed that metformin reverses DNA CpG hypomethylation and restores H3K27me3 in mutant HSPCs, thereby attenuating their survival advantage (Figure 1). Independently, George Vassiliou's team demonstrated that metformin or inhibition of mitochondrial enzyme citrate/malate transporter (SLC25A1, elevated in mutant cells) elevates 5-methylcytosine (5mC) levels, reinforcing DNA methylation in mutant HSPC. Crucially, analysis of UK Biobank data from 412,234 participants (11,190 metformin users) revealed a 51% reduced risk of *DNMT3A*^{R882}-driven CH in metformin-treated individuals compared to non-users.

The strategy of metformin intervention in AML, as proposed by these studies, holds significant promise, underpinned by three core strengths. First, it achieves precision targeting of *DNMT3A*^{R882} mutation-driven metabolic and epigenetic dysregulation, directly addressing key drivers of clonal expansion. Second, metformin offers compelling clinical advantages, including a well-established safety profile, cost-effectiveness, and global accessibility—features that position it as an ideal candidate for rapid clinical translation. Third, UK Biobank data suggest early intervention potential, hinting at efficacy during the nascent stages of CH before overt disease progression. However, significant challenges persist. Non-R882 mutations may not rely on OXPHOS, resulting in insufficient selectivity of metformin. Moreover, long-term therapeutic risks loom, including mitochondrial adaptation, compensatory pathways, and drug resistance, particularly with sustained inhibition. Additionally, observational biases in UK Biobank data cannot fully exclude confounders such as body mass index or diabetes comorbidity, underscoring the need for mechanistic validation. To advance this strategy, three priorities emerge. First, precision patient stratification—leveraging R882 mutation status and metabolic profiling—will optimize responder identification. Second, rational dosing paradigms must balance OXPHOS inhibition (for efficacy) with mitochondrial reserve preservation (for safety). Finally, conducting prospective randomized controlled trials (RCTs) to validate causal relationships and explore combination therapies for enhanced therapeutic outcomes.

TRANSLATIONAL IMPLICATIONS

Metformin, a derivative of a natural compound, has been widely used as a first-line clinical drug since its approval in 1957. It lowers blood glucose by reducing hepatic glucose production, enhances peripheral insulin sensitivity, and delays intestinal glucose absorption. Recent global clinical studies reveal that metformin not only manages hyperglycemia but also alleviates fatty liver disease, protects cardiovascular health, suppresses tumor growth, and potentially mitigates diabetes-associated malignancies. Dr. Guanghui Liu's group demonstrates that long-term metformin treatment in aged cynomolgus monkeys significantly reverses biological age, accompanied by the reduced senescent cell burden and chronic inflammation.[3] These findings suggest metformin may not only reverse aging but also lower risks of aging-related CH and AML. Notably, aging-related intestinal barrier dysfunction activates the ADP-heptose-ALPK1-TIFA-NF-κB signaling pathway, which specifically drives the expansion of *Dnmt3a*-mutant pre-leukemic cells and systemic inflammation.[4] This discovery highlights gut microbiota as novel mechanism underlying age-related CH. Given that metformin could reshape gut microbiota, its potential to suppress R882 mutation-induced clonal expansion via microbial pathways warrants further investigation.

CONCLUSION, LIMITATIONS, AND PROSPECT

These studies highlight metformin's potential roles as a precision therapeutic tool targeting genetically altered HSCs. Although these findings mark a significant step toward understanding metformin's broader pharmacological roles, further research is still required to fully elucidate its therapeutic implications, evaluate its safety and efficacy in human patients, particularly for DNMT3A-related hematologic disorders, and validate preclinical results in clinical trials. A *Nature* study by Weinstock *et al.* published in 2023 reveals that aberrant TCL1A activation promotes CH driven by *TET2* or *ASXL1* mutations but has no effect on *DNMT3A* mutation-linked CH. Given the strong association between *TET2*-mutant CH and non-small cell lung cancer (NSCLC),[5] metformin's potential roles in mutation-specific CH and other tumors warrants precise multi-omics analysis to guide future clinical precision therapies. Whether these mutants exist in natural populations should be considered. The structural interactions between the proteins containing these mutants and metformin and its downstream signaling still need further exploration.

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All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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