

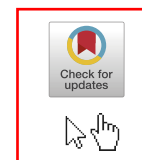


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Inhibition of mitochondrial complex III induces differentiation in acute myeloid leukemia

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ABSTRACT

Although acute myeloid leukemia (AML) is a highly heterogeneous disease with diverse genetic subsets, one hallmark of AML blasts is myeloid differentiation blockade. Extensive evidence has indicated that differentiation induction therapy represents a promising treatment strategy. Here, we identified that the pharmacological inhibition of the mitochondrial electron transport chain (ETC) complex III by antimycin A inhibits proliferation and promotes cellular differentiation of AML cells. Mechanistically, we showed that the inhibition of dihydroorotate dehydrogenase (DHODH), a rate-limiting enzyme in *de novo* pyrimidine biosynthesis, is involved in antimycin A-induced differentiation. The activity of antimycin A could be reversed by supplement of excessive amounts of exogenous uridine as well as orotic acid, the product of DHODH. Furthermore, we also found that complex III inhibition exerts a synergistic effect in differentiation induction combined with DHODH inhibitor brequinar as well as with the pyrimidine salvage pathway inhibitor dipyridamole. Collectively, our study uncovered the link between mitochondrial complex III and AML differentiation and may provide further insight into the potential application of mitochondrial complex III inhibitor as a mono or combination treatment in differentiation therapy of AML.

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1. Introduction

Acute myeloid leukemia (AML), the most common type of acute leukemia in adults, is a fatal disease with poor prognosis especially for elder patients [1,2]. The prognosis of elderly AML patients is much lower than younger patients, among people aged 60 or older, the 5-year overall survival is <25% [3,4]. AML can occur in any age

group, however, its incidence increases with age and becomes a big concern for elderly patients. The most fundamental chemotherapy backbone, cytarabine combination with anthracycline, has remained unchanged for several decades [5,6]. Due to that elder people with AML are less tolerant to the high-density chemotherapy, novel therapeutic strategies for AML are needed.

One hallmark of AML is that leukemic blast is arrested at the early differentiation stage and therapies which can overcome the differentiation blockade could be effective in AML treatment [7–9]. Acute promyelocytic leukemia (APL) represents ~10% of all AML, characterized by a specific chromosomal translocation of t(15; 17) and the resulting fusion protein, promyelocytic leukemia protein (PML)-retinoic acid receptor- α (RAR α) [10,11]. Treating APL patients with all-trans retinoic acid (ATRA) and arsenic trioxide overcomes differentiation arrest caused by PML-RAR α fusion protein, making the disease curable with the overall survival rates achieving 80%–90% [12,13]. However, other AML subtypes are still in great need to

Abbreviations: AML, acute myeloid leukemia; ETC, mitochondrial electron transport chain; DHODH, dihydroorotate dehydrogenase; AMA, antimycin A.

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