

## Research Highlight

## Novel agents inhibit human leukemic cells

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Ouabain (OUA) and pyrithione zinc (PZ) have been proved as the potential drugs for treating acute myeloid leukemia (AML). Selected from a screening among 1040 Food and Drug Administration-approved pharmacological agents, both drugs show ability to induce apoptosis of the culturing AML cells, exhibiting the poisoning effect on the cells. Studies also reveal the efficiency of the drugs in inhibiting the growth of human AML cells injected into the mice lacking of immunity and killing primary AML cells from the peripheral blood of AML patients<sup>[1]</sup>.

AML is a quickly progressive malignant disease characterized by too many immature blood-forming cells in the bone marrow and blood which interfere with the production of normal blood cells. In normal process of the formation and development of blood cells, a normal cell is gradually matured from immature blood-forming cells without uncontrolled growth. However, a single malignant AML cell accumulates genetic and/or epigenetic changes which “freeze” the cell in its immature state and prevent differentiation in AML<sup>[2]</sup>. When this is combined with other abnormal changes which disrupt genes controlling proliferation, the result

is uncontrolled proliferation and/or abnormal survival of an immature clone of cells, leading to the clinical entity of AML<sup>[3]</sup>. The malignant cell often possesses surface marker CD34, a marker of primitive blood cells<sup>[4]</sup>. Therefore, to eliminate the malignant cells, a successful drug treatment of AML has to inhibit cell proliferation and/or induce cell death including apoptosis and necrosis. Since gene regulatory networks that govern these malignant cells are very complicated, the discovery of drugs that have different targets on AML cells is an attractive but difficult endeavor<sup>[5]</sup>.

The conventional drugs for AML treatment such as cytarabine, idarubicin or daunorubicin target the cell cycle or nuclear DNA. They are not effective against the CD34<sup>+</sup> malignant cells which are usually the quiescent cells. In addition, it is found that the nuclear factor- $\kappa$ B (NF- $\kappa$ B) transcription factor is aberrantly activated in CD34<sup>+</sup> malignant AML cells to support abnormal proliferation and resistance to apoptosis triggered by therapeutic agents, suggesting that NF- $\kappa$ B inhibition may be an important therapeutic target<sup>[6]</sup>. In other tumors, loss of NF- $\kappa$ B is associated with increased apoptosis and sensitivity to chemotherapy. However, the commonly used AML chemotherapeutics (eg, cytarabine and anthracyclines) actually activate, rather than inhibit, NF- $\kappa$ B, providing a survival advantage to the malignant cells<sup>[7]</sup>. Overall, it is urgent to ask for novel drug options targeting AML cells independent of cell cycle or

nuclear DNA, relating to NF- $\kappa$ B activity and the CD34<sup>+</sup> malignant cells. Recently, Tailler *et al*<sup>[1]</sup> report that they have created a system, suitable to screen more than 1000 compounds in one single experiment, and successfully identified two potential drugs inducing AML cell death by this way.

OUA, a specific ligand of Na<sup>+</sup>/K<sup>+</sup> ATPase, has been used for more than 200 years for the treatment of cardiac insufficiency by inhibiting Na<sup>+</sup>/K<sup>+</sup> ATPase activity. In addition to this effect, recent studies have indicated that OUA is also able to induce apoptosis and inhibit cell proliferation in solid tumors, the mechanisms involved include its binding to the Na<sup>+</sup>/K<sup>+</sup> ATPase resulting in intracellular Na<sup>+</sup> and Ca<sup>2+</sup> levels increment and a variety of mechanisms mostly to be irrelevant for AML cells<sup>[8]</sup>. PZ is an antifungal and antibacterial agent for external use in clinic. Tailler *et al*<sup>[1]</sup> find that both OUA and PZ can trigger AML cell death by inhibiting NF- $\kappa$ B dependent survival signaling and hence stimulating mitochondrial pathway of apoptosis. Moreover, both OUA and PZ can inhibit the tumor formation of human AML cells injected into the mice lacking of immunity and induce the death of CD34<sup>+</sup> malignant cells from AML patients. Therefore, they conclude that, unlike the conventional drugs, both OUA and PZ exert significant anticancer effects on human AML cells by the mechanisms that are not involved with DNA damage, cell cycle arrest or differentiation, reactive oxygen species (ROS)

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increment and protein structural change. They also demonstrate that both OUA and PZ had no significant toxicity on the mice at doses which bring about high antileukemic efficiency and no synergistic effect with the conventional drugs.

The findings by Tailler *et al.*<sup>[1]</sup> in the experimental and preclinical AML treatments with OUA and PZ serve to highlight two promising antileukemic agents whose activity should be evaluated in prospective clinical studies. However, it is necessary to clarify some related preliminary questions. First, it is not enough to conclude that OUA and PZ induce apoptosis through a mechanism independently of ROS in AML cells, only by the result that inhibiting the nitric oxide synthesis failed to suppress OUA- or PZ-induced apoptosis. It needs further confirmation that no other kinds of ROS such as hydroxyl radical and superoxide anion radical involved, by FACS analysis of generation of ROS in

AML cells treated with OUA or PZ. Second, the doses of the drugs used in AML patients for effectively killing the malignant cells with no toxicity should be determined, which may quite different from that used in mice. Third, the precise antileukemic mode of action of PZ should be elucidated, and pharmacokinetics experiments of PZ should be done when it is for internal use. In addition to testing the new therapeutics, researchers should be able to explain, if it is not by chance or not due to their structure, the pharmacological reason that these two drugs with different medical usage have the same cell death-inducing effects on AML cells with similar underline mechanisms.

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