Molecular mechanisms behind AICAr drug; impact on ALL

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AICAr (5-amino-4-imidazolecarboxamide riboside, also called Acadesine) has been found to inhibit cell proliferation and has cytotoxic potential for childhood acute lymphoblastic leukemia (ALL) cells. Much of the drug's cytotoxic mechanisms, however, remain unknown. A new study published in *The FASEB Journal* explores the mechanisms behind AICAr.

Specifically, the study sought to determine: 1) whether AMP-activated protein kinase (AMPK) was necessary for the cytotoxic effects of AICAr; and 2) if AICAr had selective effects on nucleotide pool balance—which is critical for cancer cell survival and growth—in childhood ALL cells. Researchers hypothesized that, just as chemotherapeutic agents cause an imbalance in cellular nucleotide pools that results in slowed tumor growth, AICAr might inhibit ALL cell proliferation by regulating nucleotide metabolism.

Using the CRISPR/Cas9 system, researchers engineered ALL cell lines to study the molecular pathway related to AICAr's cytotoxicity. By knocking out Tumor Protein P53 (TP53) and PRKAA1 (Protein Kinase AMP-Activated Catalytic Subunit Alpha 1) in NALM-6 and Reh cell lines, researchers were able to confirm that Acadesine's inhibition of cell proliferation was independent of AMPK activation, but dependent on P53. The researchers then used a liquid chromatography tandem-mass spectrometry system to demonstrate that the drug does indeed generate nucleotide imbalances.

"To our knowledge, this is the first time that the detailed molecular mechanisms of AICAr's cytotoxicity have been carefully characterized in ALL," explained Bin-Bing S. Zhou, Ph.D., director of the Key Laboratory of Pediatric Hematology and Oncology Ministry of Health, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine. "With acute lymphoblastic leukemia being the most common form of childhood leukemia, it is our hope that clinical application of AICAr might one day lead to improved cancer therapy."

"Oncologists treating ALL have had this drug on their radar screen for some time and this study advances its mode of action, key to the realization of its full clinical potential," said Thoru Pederson, Ph.D., Editor-in-Chief of *The FASEB Journal*.

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