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Inventive combination of research approaches identifies new target for treating leukemia

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New research integrates sophisticated interdisciplinary approaches to solve a molecular mystery that may lead to alternative therapeutic strategies for acute myeloid leukemia (AML). The study, published by Cell Press in the October issue of the journal *Cancer Cell*, identifies a previously unrecognized AML target that responds well to pharmacological inhibition and may be an excellent candidate for use in future clinical trials.

AML is a type of blood cancer that disrupts normal blood cell production. "Long term survival for patients with AML remains poor despite dose-intensive chemotherapy regimens," explains senior study author, Dr. Kimberly Stegmaier from Dana-Farber Cancer Institute, Broad Institute of Harvard and MIT, and Children's Hospital Boston. "For older adults, long-term survival is dismal, and many older patients are unable to tolerate standard cytotoxic therapy." Unfortunately, identification of new treatment strategies has proven difficult as many potential targets are proteins that do not respond well to standard pharmacological methods.

Another challenge has been to unravel the molecular mechanisms associated with compounds that inhibit or reverse AML progression. Target identification is necessary for optimization of drug treatment. Dr. Stegmaier and colleagues had previously demonstrated that epidermal growth factor receptor (EGFR) inhibitors exhibited anti-AML activity.

However, this finding was somewhat puzzling as EGFR is not expressed in AML. The researchers made use of sophisticated cross-disciplinary approaches to study gene expression (genomics) and protein structure and function (proteomics) to elucidate the molecular basis for the effect of EGFR inhibitors in AML.

Spleen tyrosine kinase (Syk) was identified as a target in AML. Syk is expressed in blood cells and is critical for proper blood cell differentiation. Recent research has implicated Syk in blood cancers, specifically lymphomas and leukemias. Genetic and pharmacological inactivation of Syk resulted in anti-AML activity in AML cell lines, primary patient samples and animal models of AML. Importantly, there are Syk inhibitors currently being tested in clinical trials.

These results identify Syk as a promising therapeutic target for treatment of AML. "With an orally available, well-tolerated Syk inhibitor currently in clinical development for other indications, our results should have immediate relevance for clinical testing of Syk inhibition in patients with AML," say Dr. Stegmaier. "Our study also validates the feasibility of integrating genetic and proteomic approaches to identify small molecules and their mechanisms of action."

Source: Cell Press (news : web)