Editorial

Data mining in acute myeloid leukemia: identification of disease biomarkers, prognostic factors, novel targets, and potential drugs

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Acute myeloid leukemia (AML) is characterized by the proliferation and accumulation of myeloid blasts in the bone marrow, peripheral blood, and other tissues with suppression of normal hematopoiesis, resulting in anemia, bleeding and susceptibility to infections (1). The clinical management and intensive pharmacological therapy of AML is a challenge due to the median age of disease incidence (over 60 years of age). For young AML patients and/or those with good performance status, allogeneic hematopoietic stem cell transplantation is a therapeutic option that may lead to long periods of remission or cure of the disease (1). Recently, a better understanding of the heterogeneity of the molecular bases of the disease has helped in the identification of new pharmacological targets and the approval of new drugs (e.g., FLT3, IDH1/IDH2 and BCL2 inhibitors) (2).

To promote rapid advances in the generation and testing of hypotheses in the context of AML, several initiatives have generated and publicly deposited genomics, epigenomics, transcriptomics, and other data, in addition to clinical, laboratory, and genetic characteristics, survival outcomes, used therapies, and *ex vivo* functional studies (*Figure 1*). Of these, the AML cohorts from The Cancer Genome Atlas (TCGA) and the Beat AML program stand out due to the quantity and quality of the data provided (3,4). Thus, data mining becomes an important tool for generating knowledge of the mechanisms involved in the pathophysiology, disease progression, and therapeutic response of AML.

In a recent issue, Sun *et al.* (5) reported five hub genes (*RHOBTB2*, *PLA2G4A*, *IL2RA*, *CSRP1*, and *OLFML2A*) with prognostic relevance using two independent AML cohorts. Furthermore, the authors used chemoinformatics tools to propose natural compounds as potential ligands for proteins resulting from these genes to modulate the biological activity of these potential new targets (5). Two points deserve to be highlighted, the identification of new targets and the use of natural compounds in AML from data mining and chemoinformatics.

In previous studies, *RHOBTB2*, *PLA2G4A*, and *OLFML2A* were indicated as novel biomarkers and independent prognostic indicators in AML (6-8), and their role as potential tumor suppressors or oncogenes has already been addressed in cancer (9-12). Similarly, in AML-independent cohorts, high *IL2RA* (also known as CD25) expression was an independent factor of shorter survival outcomes, especially in the core binding factor and intermediate-risk AML groups (13-16). From a functional point of view, IL2RA acts on proliferation, differentiation, apoptosis, stem cell-related properties, and promotes leukemogenesis (17). On the other hand, the role of *CSRP1* is still little known in AML, but its role as a potential

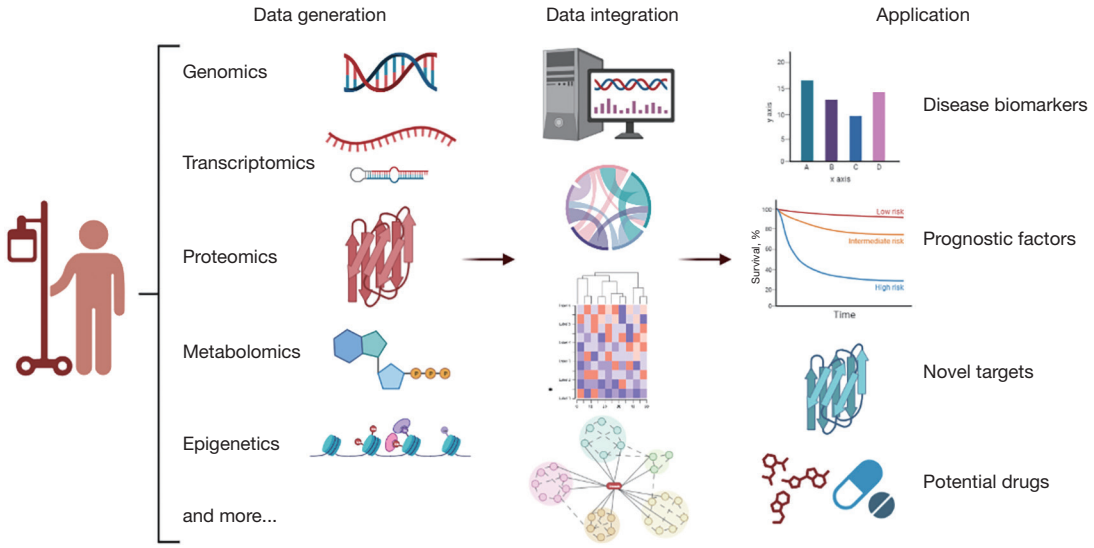

Figure 1 Data mining in acute myeloid leukemia for identification of disease biomarkers, prognostic factors, novel targets, and potential drugs. Several scientific initiatives have generated and publicly deposited genomics, epigenomics, transcriptomics, and other data, in addition to clinical, laboratory and genetic characteristics, survival outcomes, used therapies, and *ex vivo* functional studies for acute myeloid leukemia patients. These data have been integrated through data mining, bioinformatics, and chemoinformatics tools, which has resulted in the identification of disease biomarkers, prognostic factors, novel targets, and potential drugs.

oncogene was recently described in solid tumors (18). Given this background, the study conducted by Sun *et al.* (5) proposes a new biomarker and consolidates some prognostic markers in AML, promoting progress in the field of study.

These and other studies have highlighted data mining as a rich source of new therapeutic opportunities. For example, a study by Lipreri da Silva *et al.* (19), which investigated genes associated with cytoskeletal regulation in AML patients from the TCGA cohort, identified four hub genes, of which EZR (Ezrin, which encodes the ezrin protein) is a druggable target. In fact, functional and molecular studies have shown that pharmacological EZR inhibitors reduce proliferation, clonal growth, and induce apoptosis in leukemic cells, proposing a new class of drugs for the treatment of this malignant neoplasm (19).

The suggestion by Sun *et al.* (5) for the use of natural products for the treatment of AML, the strategy is interesting and deserves future studies in experimental models of AML. Historically, natural compounds have been used by mankind for centuries as a treatment for a myriad of health issues. Many reports on the use of these substances by ancient civilizations such as the populations of Mesopotamia and Egypt dating back over 2,000 years BC (before Christ), are well recognized by mankind (20). These natural compounds have several pharmacological properties such as antineoplastic, antibiotics, antivirals, fungicides, and others. Between 1981 and 2019, approximately one-third of the drugs used in the treatment of cancer were derived from natural products, reinforcing the importance of this source of new molecules (20). Cytarabine, for example, was one of the first antineoplastic drugs used in modern medicine. It was first isolated from a marine sponge, called *Cryptothethya crypta* in 1959 (21). Another example is daunorubicin, which was derived from a fungus known as *Streptomyces peucetius* in the 1970s (22). For years, these two drugs represented the mainstay in the treatment of patients with AML, known as 7+3 regimen (23). In AML, the goal of the intensive remission induction regimen is to eliminate the large burden of leukemic blasts from the bone marrow and reestablish normal hematopoiesis. Traditionally, the 7-day regimen of cytarabine plus 3-day daunorubicin (7+3) has been the standard protocol internationally for at least five decades, which has been successful in achieving complete responses in 40–60% in adults and elderly patients, and 60–80% in young patients, varying according to genetic risk stratification (23).

In addition to the historical use of natural (or inspired by) products as the basis of AML therapy, recent research has demonstrated the potential of this source of new anti-leukemic compounds. In a systematic review, Hwang

et al. (24) highlighted the classes alkaloids, carotenoids, nitrogen-containing compounds, organosulfur compounds, and phenolics as promising antineoplastic agents in this context. Similarly, Siveen *et al.* (25) highlighted some natural products (i.e., parthenolide, triptolide, cantharidin, cyclopamine, salinomycin, 17-AA, kinetin riboside, resveratrol, and avocatin B) as capable of acting at the level of leukemia-stem cells, a cell population characterized by their self-renewal capability, unlimited repopulating potential and prolonged residence in the G_0/G_1 phase of cell cycle (quiescent), which makes it difficult to be achieved by current chemotherapy regimens. Furthermore, pre-clinical studies have supported the use of natural compounds in synergy with recent frontline therapies such as venetoclax (a BCL2 inhibitor) in AML.

In summary, the study by Sun *et al.* (5) identified/consolidated biomarkers and prognostic factors in AML, in addition to suggesting new potential compounds of natural origin as disease modulators for the therapy of this aggressive blood cancer. Together these findings reinforce the integration of data mining, bioinformatics, and chemoinformatics as a promising strategy in oncology.

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Footnote

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