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Short Communication

Short Communication on "Histone Modification Patterns using RPPA-Based Profiling Predict Outcome in Acute Myeloid Leukemia Patients"

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ABSTRACT

Acute Myeloid Leukemia (AML) is a hematological malignancy with poor survival outcomes in children and adults. There is a need to enhance AML patient risk stratification to improve clinical outcomes. Precision medicine approaches that focus on the identification of patient-specific biomarkers are currently in development to improve diagnostics and treatment of cancer. Here, we comment on our studies showing the clinical significance of histone and chromatin modifier proteins in AML. Using proteomics, we identified novel subsets of adult AML patients with epigenetically distinct protein profiles that have clinical impact. More recently we discovered that overexpression of similar proteins also seems to predict poor prognosis in pediatric AML, as well as that epigenetic proteins form prognostic clusters in chronic lymphocytic leukemia. In this commentary we focus on how we can improve precision medicine in leukemia by targeting the epigenetic landscape based on proteomics in clinical practice.

Keywords: Precision medicine; Proteomics; Hypomethylating agents; Histone deacetylase inhibitors

DESCRIPTION

Acute Myeloid Leukemia (AML) is a clonal and hematological disorder of the poorly differentiated early progenitor cells ("blasts") in the bone marrow. Although AML is a disease that strongly increases with age, it affects both children and adults. Standard care employs the combination of chemotherapies and/or Stem Cell Transplantation (SCT), resulting in Overall Survival (OS) rates of 60%-70% in children, 35%-40% in adults below the age of 60, and only 5%-15% for those above the age of 60. Even with the current WHO classification system, outcomes are hard to predict for patients without certain cytogenetic and molecular features or clinical risk factors. This indicates the need for better, and more individualized treatment paradigms and improved risk-stratification.

Targeted anticancer therapies, affecting the molecular landscape, are becoming an exciting strategy to treat AML [1,2]. Many of these novel and target-focused components attack proteins rather than genetics. Therefore, analyzing the proteomic landscape may improve prognostication and therapeutic guidance in AML. One class of proteins that can be targeted includes proteins that modify epigenetics. Epigenetic modification influences the genomic structure and gene expression regulation without changing the genomic DNA code itself. They are considered an interesting therapeutic target because changes are reversible by definition [3]. Current epigenetic treatment options in cancer include Hypomethylating Agents (HMA) and Histone Deacetylase Inhibitors (HDACI). Methylation of DNA causes silencing of genes, thereby reprograming cells toward a cancer state; the HMA azacytidine and decitabine remove these methylation marks and return cells toward a more normal-like state. In AML, they are mainly used in elderly patients who are ineligible for intensive treatment such as SCT. The advantage of the use of HMA in elder patients is that side effects are relatively well-tolerated. HDACI worked by inhibiting histone deacetylase, resulting in a more transcriptionally silenced chromatin.

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Although they have been intensively studied in AML, their success remains limited [4].

In our first study focused on histone and chromatin modifying proteins in 205 adult AML patients, we found that epigenetically involved proteins express in recurrent patterns and that these correlate with outcome regardless of their cytogenetic profile, or DNA methylation related mutations [5]. Patients with high expression of these proteins were associated with relatively high white blood counts and peripheral blasts percentages, demonstrating higher proliferative potential. They also had greater resistance to therapy and shortest OS. Recently, we made a similar observation in a cohort of 483 pediatric AML patients, showing that relative high expression of histone and chromatin modifying enzymes was associated with increased relapse risk compared to low expressors. Noteworthy is that we discovered that patients with these permissive expression level profiles significantly benefitted from additional proteasome inhibition. Two more recent studies revealed global loss of the methylation mark H3K27me3 as an independent clinical predictor for adverse outcome in adult AML and CLL (manuscript in preparation). Based on these studies, we suggest that analyzing epigenetic modifying proteins can enhance risk stratification and assist with therapy selection. Further analysis of the anticipated consequences of the overexpressed proteins should be performed to provide insight into the exact mechanism of why this protein state confers greater chemo resistance and an adverse prognosis. Future experiments evaluating sensitivity to epigenetic agents associated with different histone and chromatin modifying protein expression patterns should be planned.

If this supposition of therapy selection appears to be working, real-time measurement at time of diagnosis of protein expression of a limited panel of proteins can potentially facilitate clinical application by identifying the right patient based on their matching protein profile. For instance, immunohistochemistry which quantifies proteins in samples fixed to slides, or enzyme-linked immunosorbent assays, that quantify protein concentration using antibodies, can be used to enable rapid classification [7,8]. Based on our findings, protein candidates include BRD4, SIRT1 and KDM1A. Preclinical studies have already demonstrated the efficacy of BRD4 inhibition in AML as these inhibit transcription of downstream genes involved in proliferation and NF-kB inflammation as well as increase apoptosis by down regulation of anti-apoptotic Bcl-2 protein [9]. Although clinical studies are underway, currently without response data available, previous studies suggest that BRD4 inhibition show synergistic effects in combination with other chemotherapeutics [9]. Unfortunately, a recent study in AML testing a small molecule inhibitor of Bromodomain and Extra-Terminal domain (BET) was discontinued early based on limited efficacy (NCT02698189). As subsets of patients with high BRD4 (part of the BET protein family) in our studies had the poorest outcome, we argue that BRD4 inhibition might have better clinical effect in this subset of patients. Furthermore, high SIRT1 expression also contributed to the adverse outcome in adult AML. SIRT1 acts as histone deacetylator for proteins including p53 and FOXO3. We advocate that exploring the value of HDAC inhibitors in those with the highest SIRT1 levels is worthier compared to those with lower levels [10]. Lastly, identification of KDM1A level at time of diagnosis might identify eligible candidates for histone lysine demethylase inhibition. Inhibitors have shown therapeutic potential and are currently being tested in clinical trials [11].

CONCLUSION

In summary, our results suggest that protein expression of histone and chromatin modifying protein expression can help to accelerate prognostication and suggest potential therapy combinations to investigate in selected groups of AML patients.

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