Proteomics: a new era in pediatric acute myeloid leukemia research

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In this issue of ‘Hematologica’, Hoff et al[1], report their findings on the proteome of selected candidates for around 500 pediatric acute myeloid leukemia patients and 30 control CD34+ samples. Over the past few years, it has become clear that proteomics evaluations are critical to fully understand tumor biology and develop promising therapies in oncology. As recently reviewed by Kwon et al [2], several studies in solid tumors have led to identification of druggable protein targets as well as protein biomarkers of prognostic relevance. Large scale efforts such as the National Cancer Institute’s Clinical Proteomics Tumor Analysis Consortium (CPTAC) program have successfully identified relevant signatures for multiple cancers [https://proteomics.cancer.gov/programs/cptac ]. Despite these efforts, proteomics profiling of hematological malignancies has been sparse and limited, especially in pediatric AML. One study evaluated a few proteins by 2D gel electrophoresis and MALDI-TOF in three pediatric AML patients [3]; another study compared 31 proteins between 16 pediatric AML patients and 5 controls [4] and we recently evaluated global proteomic profiles of 16 pediatric AML patients [5]. We applaud the authors for collecting, analyzing, and sharing these data for a very large cohort of patients with uniform treatment under a large cooperative group clinical trial protocol. The pediatric AML research community will gain valuable insights from these results and data for decades to come.

This article reports the results of profiling 296 candidate proteins by reverse phase protein arrays (RRPA); a technology this team has previously shown to obtain reliable data that is robust against technical preanalytical factors such as shipping, transit time, and temperature [6]. Using their own MetaGalaxy [https://www.leukemiaatlas.org/code] and progenyClust methods[7] the authors compressed these 296 individual protein variables into 31 biologically annotated protein function group variables and then 12 protein constellation variables to eventually assign each patient to one of 9 protein signature classes. Intriguingly, their downstream analyses find that one protein signature class of patients that have better outcomes with ADE+Bortezimib than with ADE alone and another protein signature class of patients that have better outcomes with ADE than with ADE+B. This suggests the tantalizing possibility that it may be possible to use proteomic evaluations to develop personalized therapy assignments. Also, some protein signature patient classes may also have reasonable targeted drug options available to them.

Additionally, the study shows that this kind of clinically vital information is unlikely to be available in RNA transcriptomic profiling. In this study, RNA expression levels typically showed a mild correlation with protein expression levels (median Pearson correlation =0.17). We obtained similar results in our pilot global proteomic study [5]. This provides motivation to systematically evaluate the global proteome in large clinical trial cohorts to uncover valuable biological and clinical insights regarding the impact of other proteins in pediatric AML.
This paper thus marks the dawn of a new era in pediatric AML multi-omics research instigating researchers to evaluate the global pediatric AML proteome and integrate its key components with relevant elements of other omics profiles, such as the transcriptomic leukemia stem cell scores (LSC17, [8] ; pLSC6[9]), prognostic transcriptomic subgroups [10] and the pediatric AML methylome [11]. In this new era, it will be imperative to develop and apply scientifically innovative and statistically rigorous data analysis method to obtain clinically and biologically useful insights based on widely reproducible results. We have incorporated subject-level bootstrap resampling of entire intact molecular profiles [12-14] into our own recent work because these methods can help to quantify the reproducibility of the results of complex multi-stage data analysis algorithms. We look forward to exploring how to incorporate the annotation-informed data reduction schemes like the one used in Meta-Galaxy into the subject-level bootstrap resampling framework of well-established statistical rigor.

Advances in the field of mass spectrometry in last couple of decades have enabled high-throughput collection of global proteomic profiles. Integrating these profiles with genomics and transcriptomics can enhance our ability to perform systems-biology based investigations to accelerate clinical translation by defining disease heterogeneity, establishing biomarkers predictive of response/relapse and last but not least identify promising novel drug targets. Though clinical translation of research discoveries is challenging, there are successful examples such as several FDA cleared/approved proteomic biomarkers currently in clinical use (predominantly immunohistochemistry or immunoassay-based testing of PSA, AFP, Her-2/neu, PR, ER, c-kit etc.) for several solid malignancies. More recently, use of FDA-approved biomarkers (as PD-L1), have enhanced the personalized use of immune checkpoint inhibitors. These advances in other malignancies warrants an urgent need to expand these strategies in pediatric cancer and specifically in hematological malignancies such as AML. As also reflected by the authors, longitudinal unbiased global proteomics studies in bulk tissue and single cells hold promise in identifying relapse/resistant clones and specifically targeting those using novel agents. Future studies are required to not only to establish and validate these biomarkers in large cohort of independent cohorts of patient but also to develop diagnostic tests with rapid turnaround to enhance the clinical translation of proteomics in making treatment decisions.

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