HEMATOLOGY

DNA methylation predicts survival in adult AML

Acute myeloid leukemia (AML) is highly fatal and most patients will relapse or die of their disease, despite recent treatment advances. Consolidative approaches such as allogenic stem cell transplantation are associated with high toxicity and treatment-related mortality; therefore, it is important to identify patients who require more-aggressive therapy and those who can be spared unnecessary treatment. A recent study has now reported the first large-scale DNA methylation outcome predictor for AML that predicts overall survival. "Our results suggest that the integration of DNA methylation data into a clinically relevant prediction model might be possible" explain Bullinger and coauthors who carried out this study.

The most important predictors of outcome include cytogenetics, a white blood cell count, age and a history of previous malignancy. Existing classification systems do not reflect the heterogeneic nature of AML. Gene-expression profiling studies revealed that genes involved in DNA methylation have differential expression, and indicate a pathogenic role for aberrant DNA methylation in distinct subgroups of AML. A novel technique based on matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was developed by the researchers to allow large-scale quantitative analysis of DNA methylation. Bullinger et al. applied this technology to analyze DNA methylation in 92 genomic regions from 182 patient samples and independently validated the results in a cohort of 74 AML samples.

The researchers performed an unsupervised two-dimensional hierarchical cluster analysis to assess the methylation of CpG units in the AML samples. The clustering of CpG units revealed two groups: one large group was characterized by low methylation levels and a smaller second group had high levels of methylation. Next the investigators evaluated the correlation between quantitative methylation patterns and prognosis. Kaplan-Meier analysis of the two groups showed significant survival outcomes according to the methylation status.

To further investigate this association, the 182 samples were randomly separated into a training set ($n = 89$) and a test set ($n = 93$), and a semisupervised approach was used to build a predictive model. This showed that good and poor outcome groups had a significantly different overall survival. The model was applied to the test set and showed that samples assigned to a good prognosis had a significantly better survival compared to those assigned to the poor prognosis group. In an independent validation set of 74 AML samples, the model also showed significant correlations with patient outcome.

The CpG units most predictive for a poor outcome were found in a region located on the long arm of chromosome 17, an area that includes homeobox genes involved in transcriptional regulation. Gene-expression profiling was used to assess a subset of 92 samples and the investigators evaluated the concordance of survival-associated outcomes between the gene-expression model and their methylation-based model. For 62% of cases, both models were in agreement. The survival of patients who had a good prognosis based on both the gene-expression and methylation-based models was associated with a significantly longer survival based on Kaplan–Meier analysis. When both models or just one model predicted a poor outcome, the probability of survival was considerably reduced.

Cox proportional hazard analysis for overall survival was used on the initial dataset ($n = 182$) as well as the independent test set ($n = 74$) to analyze the impact of the methylation-based outcome predictor on prognosis. The final model included the methylation-based outcome predictor along with FLT3 internal tandem duplication mutational status, cytogenetic risk classification and age as predictors. The researchers comment "Our data suggest that expression in [the CpG] genomic area might be down-regulated via selective DNA methylation. Using a semisupervised approach, we were able to build a predictive model based on quantitative methylation patterns". Importantly, this research shows that for adult patients with AML, a combination of DNA methylation and gene-expression-based outcome predictors can further improve prognostication.

Mathias Ehrich, the corresponding author of the study, commented "It is certainly most remarkable that the assessment of DNA methylation does add predictive value to clinical as well as molecular genetic markers. I also believe that, because this was a candidate gene approach, which is limited in the number of regions that can be investigated, it is likely that future efforts can identify genomic regions with even higher predictive power".

In summary, this research has identified the first large-scale predictor of overall survival in AML based on the methylation patterns of multiple genomic targets.

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