The epigenomic landscape of adult de novo AMLs

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Abstract

Acute myeloid leukemia (AML) is a malignant disorder, consisting of a heterogeneous group of clonal hematopoietic stem cell neoplasms. AML is characterized by aberrant accumulation of immature myelocytes in the bone marrow, which interferes with the production of normal blood cells like monocytes and neutrophils. Although great advances have been made in treatment optimization only 20% of patients obtain long term effective cure. This is mainly due to the current lack of accurately predicting optimal drug response and the absence of markers that allow personalized treatment protocols. AML is also an epigenetic disease with all AMLs suggested to display aberrant chromatin features and over 25% of patients harbouring mutations in epigenetic enzymes. The enzymes that set these histone modifications have gained great interest for targeted drug development with numerous epi-drugs becoming available over recent years. Here, we have explored the histone modification profiles, transcriptome, accessibility and DNA methylome of ~40 primary AML blasts that mutational represent the entire spectrum of AMLs, including translocations (e.g. t(15;17), t(8;21), inv(16) and 11q23), clinical markers (e.g. FLT3, NPM1) and epigenetic enzymes (e.g. IDH, DNMT3A, TET). Our analysis revealed epigenomic modification patterns that can classify these AMLs. In particular, AMLs harbouring a normal karyotype and NPM1 mutations define an epigenetic subclass of AMLs, which resembles normal CD34+ cell populations and is characterized by expression of specific novel transcripts. Comparison with normal cell types allowed further classification of AMLs in subgroups resembling progenitor populations or more differentiated cell types. In addition, this analysis revealed the pathways blocked in AML that prevent differentiation towards monocytes/neutrophils. Finally, we identified the transcription factor programs that are associated with regulating the epigenetic changes in AML. Together our results show that the interplay of the epigenome and transcription factors maintains the leukemic potential of AML cells.