TRANSCRIPTOME ANALYSES REVEAL NEW MARKERS FOR THE DIAGNOSIS AND TREATMENT OF KMT2A (MLL)-REARRANGED LEUKEMIA

BA Lopes [a,α], CP Poubel [a,α], CE Teixeira [b], A Caye-Eude [c], H Cavé [c], C Meyer [d], R Marschalek [d], M Boroni [b], M Emerenciano [a]

[a] *Acute Leukemia RioSearch Group, Division of Clinical Research, Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brazil*
[b] *Bioinformatics and Computational Biology Laboratory, Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brazil*
[c] *Department of Genetics, AP-HP Robert Debré, Paris Diderot University, Paris, France*
[d] *DCAL/Institute of Pharmaceutical Biology, Goethe-University Frankfurt, Frankfurt, Germany*

Introduction: *KMT2A* (*MLL*) gene rearrangements (*KMT2A* -r) are associated with diverse acute leukemias. Given the high number of *KMT2A* fusions, screening methods guide their detection regardless of partner gene. For instance, immunophenotyping using an anti-CSPG4 (NG2) antibody or split-signal fluorescence in situ hybridization (FISH) are routinely used for the identification of *KMT2A* -r. However, we recently revealed that certain *KMT2A* fusions (e.g. *KMT2A-USP2*) might be underestimated because tradicional methods often fail to detect them. Therefore, complementary methods are needed for appropriate detection of *KMT2A* -r. In addition, the standard treatment of *KMT2A* -r acute leukemias has not significantly improved outcomes, despite many years of international efforts. Thus, the urgent need for novel therapeutic strategies is unquestionable. **Objectives:** Here we use a machine-learning model to unravel the most appropriate markers for prediction of *KMT2A* -r in all types of acute leukemia: AML, B-ALL, T-ALL, and ALAL. We also apply differential expression analysis using RNA-seq data to point out new therapeutic possibilities for *KMT2A* -r leukemia. **Methodology:** Our analyses were performed on gene expression data from the TARGET project (n = 706; 73 *KMT2A* -r and 633 *KMT2A* -WT). We applied the BorutaSHAP variable selection to identify relevant predictors of *KMT2A* -r. After dividing our dataset into training (70%) and testing (30%) cohorts, a random forest model was trained for estimating *KMT2A* -r. Then, we performed an external validation in two independent cohorts: AML samples (n = 151) from the TCGA database, and ALL samples (n = 176) from the AP-HP, France. For the investigation of therapeutic targets and new drugs for *KMT2A* -r patients, we identified differentially expressed genes using RNA-seq data. Then, we performed pathway enrichment analysis and selection of candidate drugs using the Drug-Gene Interaction database, and overlapped results with the Genomics of Drug Sensitivity in Cancer database. **Results:** Our results revealed a set of 25 genes capable of accurately estimating *KMT2A* -r. They were significantly enriched in transcriptional misregulation in cancer (FDR ≤ 0.05). The oversampling method had the best combination of AUC, accuracy, sensitivity and specificity (0.931, 0.943, 0.917, 0.947, respectively) for estimating *KMT2A* -r. In other words, our model was able to predict 22 of 24 *KMT2A* -r patients and 178 of 188 *KMT2A* -WT patients. In the validation analyses, our model was able to correctly predict all eight *KMT2A* -r in AML (sensitivity = 1.000), but misclassified five of 11 *KMT2A* -r in ALL (sensitivity = 0.545). The *LPAR3*, *SKIDA1*, and *MEIS1* overexpression were best associated with *KMT2A* -r compared to *CSPG4* (*NG* 2), regardless of the type of acute leukemia. Of importance, high expression levels of *LPAR3* estimated the occurrence of all *KMT2A-USP2* fusions. Also, we identified 116 up-regulated genes in relapsed *KMT2A* -r acute leukemia, and 56 drug interactions with 13 genes. The *KMT2A* -r cell lines were more sensitive to foretinib treatment (Wilcoxon, p = 0.019) compared to *KMT2A* -WT. **Conclusions:** In this study, we observed that our algorithm provided highly accurate predictions for *KMT2A* -r acute leukemias. Therefore, we provide valuable options for screening *KMT2A* -r in leukemia, including *LPAR3*, *SKIDA1*, and *MEIS1* overexpression. We also reveal that foretinib should be further investigated as a therapeutic alternative in *KMT2A* -r acute leukemia.

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TRANSFORMAÇÃO LEUCÊMICA DE DOENÇA MIELOPROLIFERATIVA CRÔNICA TRIPLO NEGATIVA. RELATO DE CASO

LG Carvalho [a], VRS Júnior [a], MCG Silva [b], VMA Bandeira [b], MP César [b], MCB Correia [a], MFH Costa [a,b]

[a] *Universidade Federal de Pernambuco (UFPE), Recife, PE, Brasil*
[b] *Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, PE, Brasil*

Introdução: As doenças mieloproliferativas crônicas BCR-ABL negativas apresentam risco de transformação leucêmica de 1- 20% em dez anos e estão relacionadas a pior prognóstico. **Objetivo:** relatar caso clínico de paciente com transformação de uma doença mieloproliferativa crônica triplo negativo em leucemia mieloide aguda. **MATERIAIS E método:** após assinatura do termo de consentimento livre e esclarecido pelo paciente, foi realizada revisão de literatura nas bases de dados (LiLacs, PubMed/Medline, BVS e Scielo) e coleta dos dados clínicos e laboratoriais através do prontuário do paciente. **Relato do caso:** Paciente de 65 anos, masculino, portador de Diabetes mellitus, apresenta quadro de perda ponderal de dez quilos em um mês e anemia com níveis de Hemoglobina de 4 g/dL, leucócitos de 47.000/μL, sendo 79% de segmentados e plaquetopenia. Havia ausência de visceromegalias ou adenomegalias ao exame físico. O aspirado medular foi sugestivo de SMD- AREB II. A biópsia de medula óssea sugeria alterações compatíveis com doença mieloproliferativa, mais próxima de uma Leucemia Mielóide Crônica. Exames de BCR-ABL, MPL, CALR e JAK 2 com resultados negativos. Foi submetido a citorredução inicial com hidroxiureia, porém evoluiu com redução do número de leucócitos para 6.000/ μL e presença de 16% de blastos em sangue periférico, realizado novo mielograma com 21% de blastos de linhagem

[α] These authors share first authorship.
[α] These authors share first authorship.