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602.MYELOID ONCOGENESIS: BASIC

Genomic Analyses Unveil the Pathogenesis and Inform on Therapeutic Targeting in *KMT2A*-PTD AML

Yasuo Kubota, MDPhD[1], *Megan Reynold*[1], *Nakisha D Williams, MBBS*[1], *Naomi Kawashima, MD PhD*[1], *Carlos Bravo-Perez, MD PhD*[2,1], *Luca Guarnera, MD*[1], *Christopher Haddad*[1], *Aashray Mandala, BS*[1], *Carmelo Gurnari, MD*[1,3], *Arda Durmaz, PhD*[1], *Valeria Visconte, PhD*[1], *Jaroslaw P. Maciejewski, MD, PhD, FACP*[1]

[1]Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[2]Department of Hematology and Medical Oncology, Hospital Universitario Morales Meseguer, University of Murcia, IMIB-Pascual Parrilla, CIBERER - Instituto de Salud Carlos III, Murcia, Spain
[3]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

A partial tandem duplication (PTD) in the *KMT2A* gene is detected in approximately 5-10% of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Previous studies revealed that HOX-genes are highly expressed in *KMT2A*-PTD AML similar to *KMT2A*-rearranged or *NPM1*-mutated AML. While the overexpression of HOX-genes is a convergent oncogenic pathway shared by these molecular subtypes of AML, the mechanism by which *KMT2A*-PTD induces high expression of the HOX-genes remains unclear and may be distinct from that mediated by balanced *KMT2A*-translocations, and *NPM1* mutations.

We stipulated that analysis of common molecular features of *KMT2A*-PTD will help identifying mechanistic intersections pointing towards possible targeted therapies. In a total of 5420 AML cases [1] including 793 cases from publicly available sources (Beat AML [2] and TCGA [3]), we identified 254 cases of *KMT2A*-PTD. Somatic mutational screening and karyotype analysis showed co-occurrence with *DNMT3A* (31%), *FLT3-ITD* (32%), *IDH1/2* (26%), *RUNX1* (28%), *TET2* (18%), *SRSF2*, *STAG2*, *U2AF1* mutations and deletion 5q. Strong leukemic initiators such as *KMT2A*-rearrangement, *CBFB-MYH11*, *PML-RARA*, *RUNX1-RUNX1T1*, trisomy 8 and *NPM1* mutations were mutually exclusive with *KMT2A*-PTD and did not rely on acquisition of additional mutations linked to secondary AML ontogenesis (*e.g.*, *ASXL1*, *RUNX1*, *SRSF2*, and *STAG2*) different from *KMT2A*-PTD.

Next, we analyzed bulk mRNA-expression between mutually exclusive *KMT2A*-PTD, *KMT2A*-rearranged or *NPM1*-mutant high HOX-genes expressors. While several differentially expressed genes (DEG) between *KMT2A*-PTD and *KMT2A*-rearranged cases were detected, there were few DEG between *KMT2A*-PTD and *NPM1*-mutated cases. Compared to *KMT2A*-rearrenged cases, *KMT2A*-PTD had higher expression of *CD34* and *KIT* in addition to some HOX-genes such as *HOXB2* or *NKX2-3*. In contrast, expression of *CD1D*, *CD14*, and immune checkpoint genes including *LILRB4*, *CD276*, *CD86*, and *SIGLEC7* was much higher in *KMT2A*-rearranged than *KMT2A*-PTD cases. These results prompted us to analyze the hematopoietic differentiation status. For this purpose, we defined three gene signatures along the HOX-targeted genes axis, termed as HOX-primitive, HOX-transient, and HOX-committed profiles. Differentiation analysis revealed almost all of *KMT2A*-PTD cases could be subclassified into HOX-transient stage while most of *KMT2A*-rearranged cases were *HOX*-committed. However, *NPM1*-mutated cases were interspersed in all the differentiation stages along the HOX-axis. We therefore assumed that there were a few DEG shared between *KMT2A*-PTD and *NPM1*-mutated cases as some *NPM1*-mutated AML clustered in the HOX-transient expression profile group.

Intriguingly, DEG analysis was concordant with the hierarchical clustering based on the HOX-gens axis. Indeed, *CD34* and *KIT* were highly expressed in the HOX-transient cases, and *CD1D* and *CD14* in the HOX-committed cases, consistent with the enrichment of *KMT2A*-PTD and *KMT2A*-rearranged AML, respectively. We can conclude that the observed signatures were unique to the HOX-stages rather than the molecular abnormalities such as *KMT2A*-PTD and *KMT2A*-rearrangements. For example, *CD34* upregulation was a feature shared transversally by all HOX-transient cases, including both *KMT2A*-rearranged and *NPM1*-mutated cases. As shown in Figure, *KMT2A*-rearranged, *KMT2A*-PTD, and *NPM1*-mutated cases were more clearly classified in HOX-profiles than molecular abnormalities. Additionally, among the cases which molecular subtypes were not clear, those with high HOX-genes expression revealed higher *MEN1* expression.

In conclusion, despite molecularly different, *KMT2A*-PTD, *KMT2A*-rearranged, and *NPM1*-mutated AML have similar expression patterns defined by each HOX differentiation stage. Like core binding factor AML such as *RUNX1-RUNX1T1* and *CBFB-*

MYH11, AML with higher expression of HOX-genes should be classified in the same group, HOX-AML. Given the results obtained with menin inhibitors in *KMT2A*-rearranged and *NPM1*-mutated AML, our findings open an opportunity for exploiting a therapeutic vulnerability in all HOX-AML including *KMT2A*-PTD AML or AML with high *MEN1* expression. Since HOX-AML highly express genes according to the HOX differentiation profile, stage-specific surface proteins coded by these genes would be promising targets.

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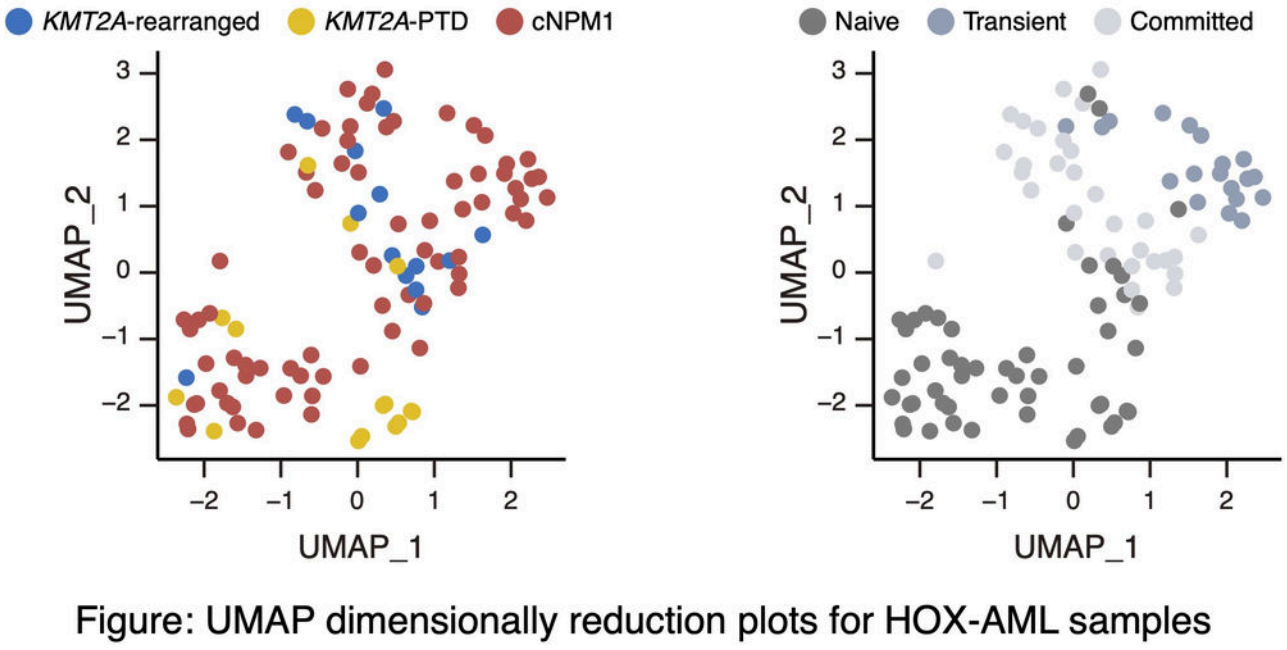

Figure: UMAP dimensionally reduction plots for HOX-AML samples

Figure 1

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