Characterization of KMT2A rearrangement in pediatric Acute Myeloid Leukemia and drug repurposing from transcriptomic data

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Introduction

KMT2A rearrangement (KMT2A-r):
- The most common structural aberrations in pediatric AML.
- Associated with poor outcome.
- Important role in the risk stratification and treatment selection.
- The disrupted pathways and the functioning mechanisms involving this gene fusion are still poorly understood.

We propose a new approach in the characterization of KMT2A-r using gene expression data and novel bioinformatic tools and we suggest new repurposed drugs as a potential treatment for pediatric AML.

Methods

Data

TARGET Pediatric AML repository

Transcriptomics

Bone Marrow

KMT2A-r patients

Healthy controls

Differential gene expression analysis

KMT2A-r gene signature

Characterization

- **Functional enrichment**: We found gene signatures over-represented in the top down-regulated or up-regulated genes. GSEA method.

- **Pathway activity**: Estimated using the expression of their target genes. Progeny database[1].

- **Transcription factor activity**: Estimated using the expression of their target genes. Dorothea database[2].

- **Signaling network reconstruction**: Using the pathway and transcription factor activities, we applied an integer linnear programing algorithm to estimate the signaling network that better represents the effect of the KMT2A rearrangement. Omnipath interaction database. Carnival pipeline[3].

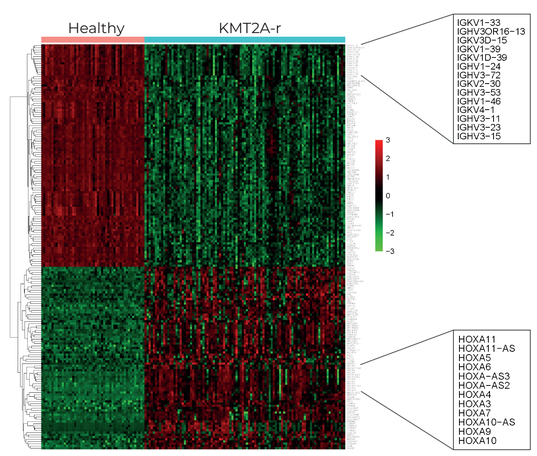
Drug repurposing

Connectivity Map L1000 database.

Compound that gave rise to an opposing gene expression signature.

Results

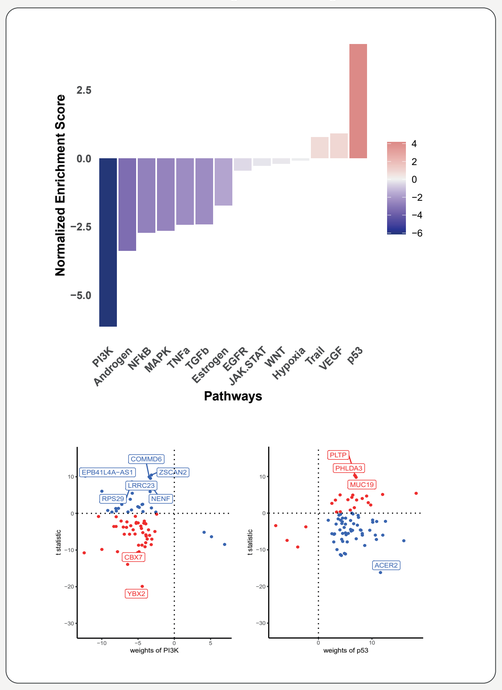
Differential expression



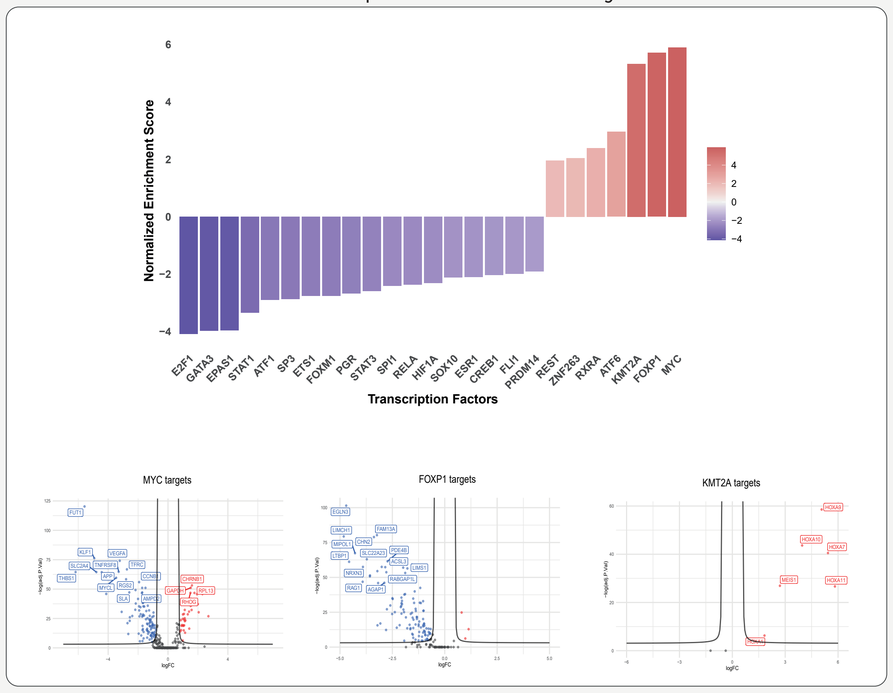
Gene Set Enrichment

Pathway	Gene ranks	NES	pval	padj
CHNG_MULTIPLE_MYELOMA_HYPERPLOID_UP		4.30	6.9e−24	1.4e−21
REACTOME_SARS_COV_2_MODULATES_HOST_TRANSLATION_MACHINERY		4.06	3.6e−23	6.7e−21
TIEN_INTESTINE_PROBIOTICS_6HR_UP		3.52	7.1e−16	8.1e−14
HOLLEMAN_VINCRISTINE_RESISTANCE_ALL_DN		3.38	1.8e−11	1.4e−09
BILANGES_SERUM_RESPONSE_TRANSLATION		3.48	3.4e−11	2.5e−09
LUI_THYROID_CANCER_CLUSTER_3		3.41	1.1e−10	8.1e−09
VALK_AML_CLUSTER_16		3.28	9.1e−10	5.5e−08
REACTOME_CRISTAE_FORMATION		3.18	2.1e−09	1.2e−07
LUI_TARGETS_OF_PAX8_PPARG_FUSION		2.99	5.7e−09	3.1e−07
WP_MITOCHONDRIAL_COMPLEX_IV_ASSEMBLY		3.15	5.7e−09	3.1e−07
REACTOME_PARASITE_INFECTION		−2.32	8.5e−31	3.8e−28
REACTOME_FCERI_MEDIATED_NF_KB_ACTIVATION		−2.26	3.0e−31	1.5e−28
REACTOME_ROLE_OF_PHOSPHOLIPIDS_IN_PHAGOCYTOSIS		−2.45	1.0e−31	5.8e−29
REACTOME_CD22_MEDIATED_BCR_REGULATION		−2.53	6.9e−32	4.4e−29
REACTOME_FCGR_ACTIVATION		−2.49	6.5e−32	4.4e−29
REACTOME_ROLE_OF_LAT2_NTAL_LAB_ON_CALCIUM_MOBILIZATION		−2.48	6.1e−32	4.4e−29
REACTOME_CREATION_OF_C4_AND_C2_ACTIVATORS		−2.52	9.9e−33	1.1e−29
REACTOME_FCERI_MEDIATED_MAPK_ACTIVATION		−2.44	1.9e−33	2.7e−30
REACTOME_BINDING_AND_UPTAKE_OF_LIGANDS_BY_SCAVENGER_RECEPTORS		−2.44	6.1e−35	1.3e−31
REACTOME_SCAVENGING_OF_HEME_FROM_PLASMA		−2.54	1.7e−35	7.4e−32

Pathway activity



Transcription Factor activity

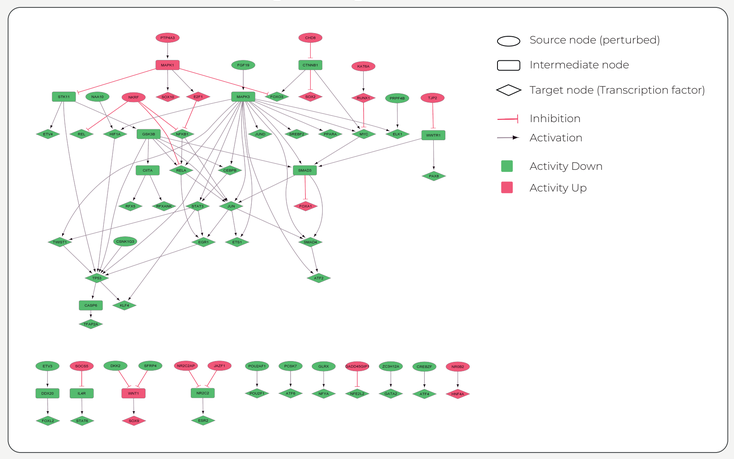


Drug repurposing

Top 10 opposite perturbagens

Score	Type	Name	Description
-98.39	Gene Knock-Down	RTCD1	-
-97.29	Gene Knock-Down	SNX11	Sorting nexins
-96.74	Gene Knock-Down	DRAP1	-
-96.22	Gene Knock-Down	ZRSR2	RNA binding motif (RRM)
-96.07	Gene Knock-Down	TRAP1	Heat shock proteins / HSPC
-95.92	Gene Knock-Down	SMNDC1	Tudor domain containing
-95.85	Compound	mebendazole	Tubulin inhibitor
-95.63	Gene Knock-Down	TCTN1	Tectonic proteins
-95.42	Gene Over-Expression	RDBP	-
-95.27	Gene Knock-Down	SACM1L	-

Signaling Network



Conclusions

- MYC and FOXP1 transcription factors had an increased activity in KMT2A-r patients and, interestingly, the TF activity of KMT2A was also increased since the HOX genes, that are positively regulated by wild type KMT2A, were overexpressed in rearranged patients.

- Downregulation of the activity of PI3K pathway, pointing to the biologic cooperativity between KMT2A fusion protein and this signaling pathway.

- We propose Mebendazole as a potential therapeutic drug in the treatment of pediatric AML patients with KMT2A-r, since it is capable of reverse the transcriptomic signature induced by this gene rearrangement.

1 Schubert M, Klinger B, Klünemann M, Sieber A, Uhlitz F, Sauer S, Garnett MJ, Blüthgen N, Saez-Rodriguez J. (2018). Perturbation-response genes reveal signaling footprints in cancer gene expression. Nature Communication, Issue 9, Nr. 20. https://doi.org/10.1038/s41467-017-02391-6.
2 Garcia-Alonso L, Holland CH, Ibrahim MM, Turei D, Saez-Rodriguez J. (2018). Benchmark and integration of resources for the estimation of human transcription factor activities. Genome Research 2019. 29: 1363-1375, https://doi.org/10.1101/gr.240663.118
3 Melas IN, Sakellaropoulos T, Iorio F, Alexopoulos L, Loh WY, Lauffenburger DA, Saez-Rodriguez J, Bai JPF. (2015). Identification of drug-specific pathways based on gene expression data: application to drug induced lung injury. Integrative Biology, Issue 7, Pages 904-920, https://doi.org/10.1039/C4IB00294F.

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