DEVELOPING TRANSCRIPTOMIC SIGNATURE FOR IDH1 AND IDH2 ACUTE LEUKEMIA AND THE DEMONSTRATION OF HIGH PREVALENCE OF THESE SIGNATURES IN MUTATION-NEGATIVE LEUKEMIA

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INTRODUCTION

Despite multiple studies, the impact of IDH1 and IDH2 (IDH1/2) mutations on the overall biology and clinical outcome of acute myeloid leukemia (AML) remains controversial and not explicitly determined. This may is likely due to the fact that AML with IDH1/2 mutations are not significantly biologically different from average AML. However, current data suggests that adding IDH inhibitors to a combination therapy improves the outcome of patients with IDH1/2 mutations. We explored transcriptional profile for cases with IDH1/2 mutations and compared to AML cases without mutations.

AIM

While the first aim is to define the transcriptional profile of IDH1/2 AML cases, we also aimed to explore if the specific IDH1/2 transcription profile can also be seen in AML cases without IDH1/2 mutations. We explored the potential of using artificial intelligence (AI) and transcriptomic data to define a specific transcriptomic signature for IDH1-positive (IDH1p) and IDH2-positive (IDH2p) AML. Then we used this signature to screen IDH1/2-negative acute myeloid leukemia (AMLn).

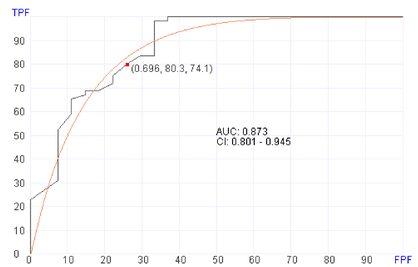
METHOD

RNA was extracted from the bone marrow samples of 1186 cases of AML or advanced myelodysplastic syndrome with increased blasts. The RNA was sequenced by next generation sequencing (NGS) using a targeted RNA panel of 1600 genes. IDH1 mutation was detected in 83 cases (7%) and IDH2 was detected in 120 (10%). A set including 83 cases with IDH1 mutation and 156 random AMLn was isolated to develop IDH1 transcriptomic signature. A second set including the 120 cases with IDH2 mutation and 180 random AMLn cases was used for developing the IDH2 transcriptomic signature. The rest of the cases were used for testing these signatures. Bayesian statistics were used to rank the genes that distinguish between two groups, then random forest was used to establish the signatures. Two thirds of the sets used for developing the signatures were used for training and one third was used for testing. A score for the combination of relevant genes with a cut-off point was established. The same Bayesian/random forest algorithm was used to test the rest of the AML cases.

RESULTS

Developing IDH1 transcriptomic Signature

8 genes: TRAF3, TRAF2, HMGB1, CDK2, LRRC59, MEAF6, CREB1, RPN.

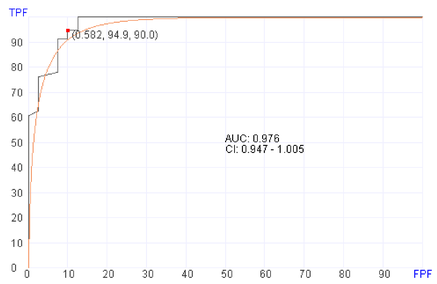


Biological Relevance of IDH1 signature genes

- Immune/inflammatory activation: HMGB1, TRAF2, TRAF3
- Transcriptional activation: CREB1.
- Proliferation execution (Cell-cycle progression): CDK2
- Proteasomal activity : RPN
- RNA-protein trafficking: LRRC59:
- Histone acytylation and gene expression : MEAF6

Developing IDH2 transcriptomic Signature

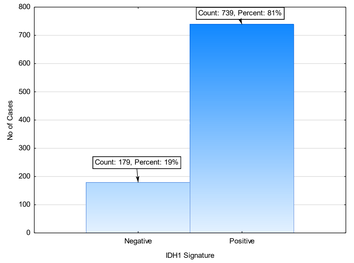
35 genes: TRAF3, TRAF2, STRN, TBX21, TRAF5, EVI2A, NAMPT, NFYC, PRPF40B, SF3A1, SMAD5, CDK2, LUC7L2, MCM3AP, PRPF8, THRA, SMC3, ACVR1, KIF5B, MDS2, RAD21, RPL21, PSIP1, JAK2, PTPA(PPP2R4), SUZ12, TCL6, RAC2, LRRC59, YWHAE, PTBP1, TPR, TMEM230, HSP90AA1, RNF217-AS1(STL).



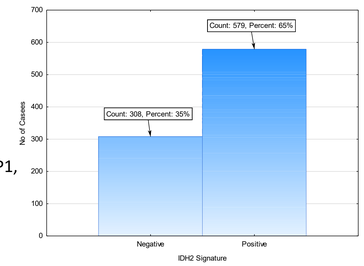
Biological Relevance of IDH2 signature genes

- RNA splicing / processing (SF3A1, PRPF8, PRPF40B, PTBP1, LUC7L2)
- Chromatin / cohesin complexes (SUZ12, SMC3, RAD21, PSIP1)
- Immune-NF-κB signaling (TRAF2/3/5, RAC2, TBX21)
- Oncogenic drivers (KIF5B, STRN, TPR, YWHAE).

81% of mutation-negative had IDH1 signature



65% of mutation-negative had IDH2 signature



Top 35 genes distinguish IDH1-positive cases

Gene	IDH1-Positive (Median)	IDH1-negative (median)	LogFDR
TRAF2	1.4605	4.3508	-Infinity
TRAF3	1.0716	4.2172	-Infinity
TRAF5	1.1872	4.358	-Infinity
RPN1	6.6193	7.1118	-12.301
CDK2	4.2887	4.8724	-12.176
FANCE	2.5989	3.3214	-10.933
MEAF6	3.9677	4.5641	-10.733
CLTA	5.9608	6.4877	-9.3768
HDAC2	4.7462	5.3278	-9.0416
PRKAR1A	6.0745	6.7528	-8.9393
BTK	4.7727	5.4268	-8.9269
C2CD2L	3.862	4.4666	-8.8005
PRKACA	4.6919	5.3091	-8.6962
PCNA	5.7658	6.397	-8.6231
PTPA	4.3241	4.8323	-8.5695
CDK7	4.6822	5.2152	-8.4825
XRCC6	6.637	7.0556	-8.3388
PSIP1	6.3599	6.9234	-8.2184
HSP90AA1	8.0577	8.5639	-8.1143
KIF5B	6.1787	6.6717	-7.9738
MYH11	0.6342	1.3356	-7.9114
CHMP2B	4.6936	5.2822	-7.8639
SET	6.8664	7.3975	-7.8251
TMEM230	4.6764	5.1495	-7.797
PPM1D	4.5207	5.046	-7.7886
STRN	4.1804	4.6622	-7.7733
SKP2	4.1348	4.7379	-7.5762
JAK2	5.3367	5.9122	-7.4847
LRRC59	5.5136	6.044	-7.4642
SMC3	6.0238	6.462	-7.4102
MSH3	4.329	4.8497	-7.2369
COMMD1	4.7824	5.2278	-7.223
WEE1	4.5009	5.0559	-7.1429
BLM	4.1564	4.708	-7.0357
THRA	2.0127	0.0186	-6.991

Top 35 genes distinguish IDH2-positive cases

Gene	IDH2-positive (Median)	IDH2-negative (Median)	LogFDR
ACVR1C	0.9798	0	-Infinity
EGFR	1.1708	0.0904	-Infinity
EVI2B	2.2585	0.0878	-Infinity
FGF9	0.9486	0.0476	-Infinity
FGFR1OP	1.5317	0	-Infinity
HAS2	0.8747	0.0499	-Infinity
LUC7L2	1.4756	0.0259	-Infinity
MAP2	0.7401	0.0378	-Infinity
MCM3AP	1.2762	0.0112	-Infinity
NAMPT	1.7003	0.1093	-Infinity
NFYC	1.0098	0.0147	-Infinity
PRPF8	1.5216	0.0401	-Infinity
RPL21	1.4071	0	-Infinity
SF3A1	1.4088	0.0212	-Infinity
SHC2	0.7877	0.031	-Infinity
SMAD5	0.9411	0.0071	-Infinity
THRA	1.0728	0.0055	-Infinity
TNFRSF17	1.4875	0.0221	-Infinity
ACVR1	0.8442	0	-12.778
DIRAS3	1.1457	0.0766	-12
CXXC4	0.7454	0.0224	-11.398
PRPF40B	0.4057	0	-11.234
DKK2	0.6848	0.0577	-11.166
TBX21	0.538	0	-10.993
RNF217-AS1	0.5262	0	-10.497
RHOD	0.6182	0.0511	-10.203
EVI2A	1.1763	0.0909	-10.077
CTRB2	0.3301	0	-9.6498
MDS2	0.4501	0	-9.5644
FZD10	0.3979	0.0053	-9.408
EPHA7	0.3177	0	-8.4015
FGF6	0.4405	0.0396	-7.988
IL3	0.5867	0.0203	-7.5764
RASGRF1	0.5687	0.0586	-6.8498
NTF3	0.2879	0	-6.3739

CONCLUSIONS

- AML with IDH1/IDH2 mutations may overlap biologically with other types of AML
- Despite this overlap, transcriptomic signatures can be developed for IDH1p and IDH2p cases using machine learning.
- Inflammatory and splicing genes play a major role in distinguishing IDH1/IDH2-positive cases.
- 80% of AML cases without IDH1 mutation show IDH1 transcription signature
- 65% of AML cases without IDH2 mutation show IDH2 transcription signature
- The data justify the performance of clinical trials adding IDH1or IDH2 inhibitors to combination therapy in patients with positive IDH1/IDH2 signatures.

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