Research Article

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Integrated regulatory and metabolic networks of the tumor microenvironment for therapeutic target prioritization

Supplemental Materials

Table S1: 177 curated drugs from the drug repurposing hub library, with the TF target, mechanism of action and various drug features discussed in the main text.

Columns correspond respectively to: drugs name, clinical phase, mechanism of action that specifies the biological mechanism (e.g., reaction or interaction) that produces the pharmacological effect, TF target, targeting disease, and other indications.

Figure S1: Clustering of the predicted enzyme fold changes when single or combinations of transcription factors in the network are targeted (rows).

Rows represent 247 unique TF-targeting perturbations from a single or pairwise combination of 177 curated drugs. TF target combinations were clustered into 5 distinct clusters using hierarchical clustering with complete distance. The fold changes are systematically displayed for the enzymes for the malignant, t-cell, macrophage, and oligodendrocyte (columns). This ordering is preserved across the different pathways: glycolysis, anaerobic glycolysis, and the flux from the glycolytic pathways to the TCA cycle.

Figure S2: Clustering of the predicted relative changes in fluxes when single or combinations of transcription factors in the network are targeted (rows).

Rows represent 247 unique TF-targeting perturbations from a single or pairwise combination of 177 curated drugs. TF target combinations were clustered into 5 distinct clusters using hierarchical clustering with complete distance. The flux changes were aggregated and are systematically displayed for the malignant, t-cell, macrophage, and oligodendrocyte (columns). This ordering is preserved across the different pathways: glycolysis, anaerobic glycolysis, and the flux from the glycolytic pathways to the TCA cycle.

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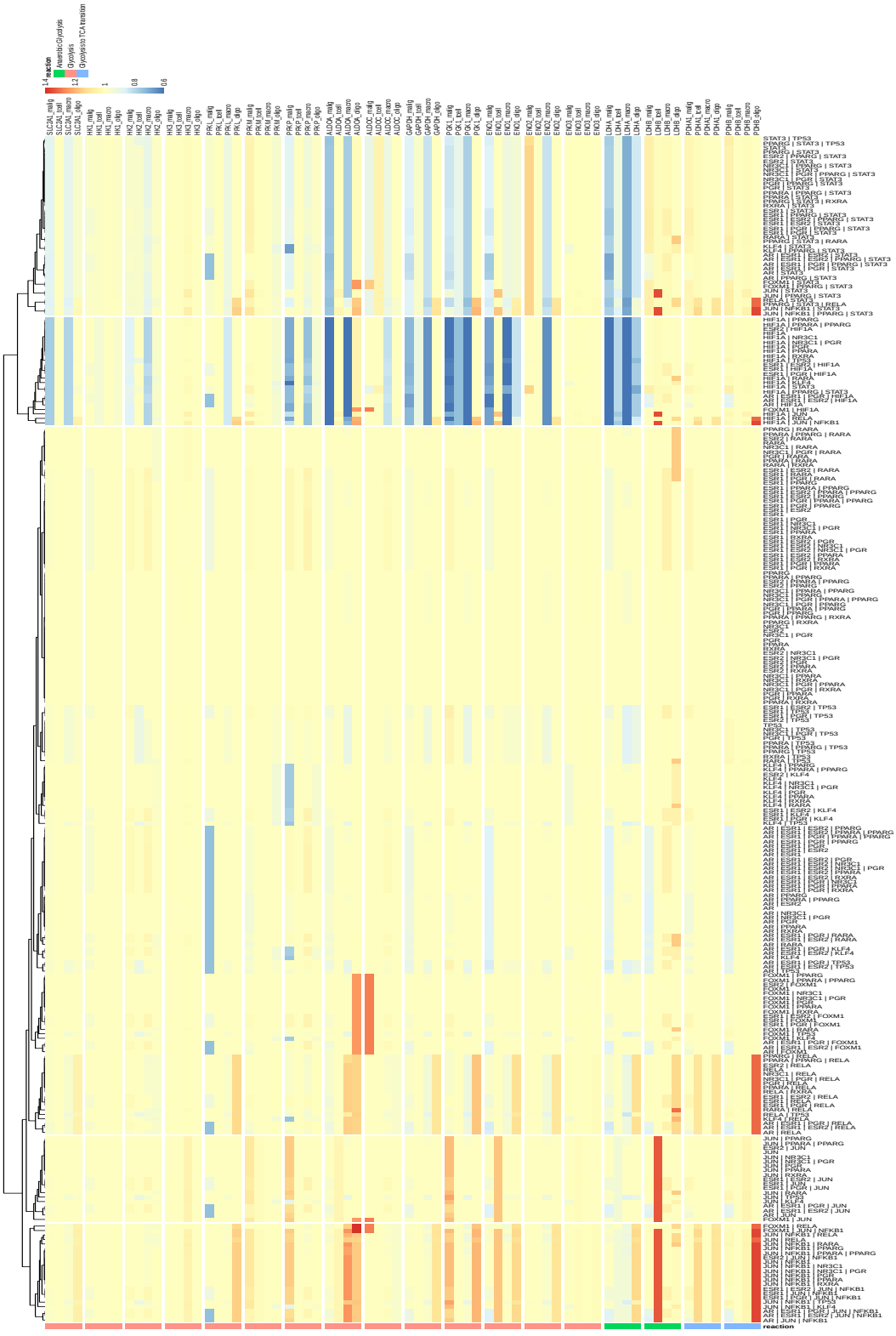
Figure S3: Sensitivity analysis results: clustering of the mean relative changes in fluxes when combinations of transcription factors in the network are targeted (rows).

Clustering of the mean of the 300 predicted relative changes in fluxes when transcription factor combinations in the network are targeted (rows). There were five distinct clusters observed. The flux changes were aggregated and are systematically displayed for the malignant, T-cell, macrophage and oligodendrocyte (columns). This ordering is preserved across the different pathways: glycolysis, anaerobic glycolysis and the flux from the glycolytic pathways to the TCA cycle (pyruvate dehydrogenase).

Figure S4: Sensitivity of glioblastoma cell lines to STAT3 inhibitors.

The data is obtained from the DepMap Portal. The drug sensitivity is measured by the log2 fold-change of cell viability. Each data point corresponds to a glioblastoma cell line. Values smaller than 0 indicates the the drug has inhibitory effect on the cell line.

Figure S1


reaction
Anaerobic Glycolysis
Glycolysis
Glycolysis to TCA transition
1.4
1.2
1
0.8
0.6
SLC2A1_mal
SLC2A1_bal
SLC2A1_macro
SLC2A1_oligo
HK1_mal
HK1_bal
HK1_macro
HK1_oligo
HK2_mal
HK2_bal
HK2_macro
HK2_oligo
HK3_mal
HK3_bal
HK3_macro
HK3_oligo
PRKL_mal
PRKL_bal
PRKL_macro
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PRKU_mal
PRKU_bal
PRKU_macro
PRKU_oligo
PRKP_mal
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ENO1_macro
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ENO2_macro
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ENO3_macro
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LDHA_bal
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LDHB_mal
LDHB_bal
LDHB_macro
LDHB_oligo
PDHAL_mal
PDHAL_bal
PDHAL_macro
PDHAL_oligo
PDHB_mal
PDHB_bal
PDHB_macro
PDHB_oligo
STAT3 | TP53
PPARG | STAT3 | TP53
STAT3
PPARG | STAT3
ESR2 | PPARG | STAT3
ESR2 | STAT3
NR3C1 | PPARG | STAT3
NR3C1 | PGR | PPARG | STAT3
NR3C1 | PGR | STAT3
PGR | PPARG | STAT3
PGR | STAT3
PPARA | PPARG | STAT3
PPARA | STAT3
PPARG | RXRA
PPARA | RXRA
ESR1 | STAT3
ESR1 | PPARG | STAT3
ESR1 | ESR2 | PPARG | STAT3
ESR1 | ESR2 | STAT3
ESR1 | PGR | PPARG | STAT3
ESR1 | PGR | STAT3
PPARA | PPARG | RARA
KLF4 | STAT3
KLF4 | PPARG | STAT3
AR | ESR1 | ESR2 | PPARG | STAT3
AR | ESR1 | PPARG | STAT3
AR | ESR1 | PGR | STAT3
AR | ESR1 | STAT3
AR | PPARG | STAT3
FOXM1 | PPARG | STAT3
JUN | STAT3
JUN | PPARG | STAT3
PPARA | STAT3 | RELA
JUN | NFKB1 | STAT3
JUN | NFKB1 | PPARG | STAT3
HIF1A | PPARG
HIF1A | PPARA | PPARG
HIF1A | HIF1A
HIF1A
HIF1A | NR3C1
HIF1A | NR3C1 | PGR
HIF1A | PPARA
HIF1A | RXRA
HIF1A | ESR2
ESR1 | HIF1A
ESR1 | HIF1A | ESR2
ESR1 | PGR | HIF1A
HIF1A | RXRA
HIF1A | STAT3
HIF1A | PPARG | STAT3
AR | ESR1 | ESR2 | HIF1A
AR | HIF1A
FOXM1 | HIF1A
HIF1A | RELA
HIF1A | JUN | NFKB1
PPARG | RARA
PPARA | PPARG | RARA
ESR2 | RARA
NR3C1
NR3C1 | RARA
NR3C1 | PGR | RARA
PGR | RARA
RARA | RXRA
ESR1 | ESR2 | RARA
ESR1 | RARA
ESR1 | PGR | RARA
ESR1 | PPARA
ESR1 | PPARA | PPARG
ESR1 | ESR2 | PPARG
ESR1 | PGR | PPARA | PPARG
ESR1 | PGR | PPARG
ESR1 | ESR2
ESR1
ESR1 | PGR
ESR1 | NR3C1
ESR1 | NR3C1 | PGR
ESR1 | PPARA
ESR1 | RXRA
ESR1 | ESR2 | PGR
ESR1 | ESR2 | NR3C1
ESR1 | ESR2 | NR3C1 | PGR
ESR1 | ESR2 | PPARA
ESR1 | ESR2 | RXRA
ESR1 | PGR | PPARA
ESR1 | PGR | RXRA
PPARG
PPARA | PPARG
ESR2 | PPARG
PPARA | PPARG | PPARG
NR3C1 | PPARA | PPARG
NR3C1 | PPARG
NR3C1 | PGR | PPARA | PPARG
PGR | PPARA | PPARG
PGR | PPARG
PPARA | PPARG | RXRA
PPARG | RXRA
ESR2
NR3C1 | PGR
PPARA
RXRA
ESR2 | NR3C1
ESR2 | NR3C1 | PGR
ESR2 | PPARA
ESR2 | RXRA
NR3C1 | PPARA
NR3C1 | PGR | PPARA
PGR | PPARA
PPARA | RXRA
ESR1 | ESR2 | TP53
ESR1 | PGR | TP53
ESR2 | TP53
TP53
NR3C1 | TP53
NR3C1 | PGR | TP53
PGR | TP53
PPARA | TP53
PPARG | PPARG | TP53
PPARG | TP53
RXRA | TP53
RARA | TP53
KLF4 | PPARA | PPARG
ESR2 | KLF4
KLF4
KLF4 | NR3C1
KLF4 | NR3C1 | PGR
KLF4 | PGR
KLF4 | PPARA
KLF4 | RARA
ESR1 | ESR2 | KLF4
ESR1 | KLF4
KLF4 | TP53
AR | ESR1 | ESR2 | PPARG
AR | ESR1 | ESR2 | PPARA | PPARG
AR | ESR1 | PPARA | PPARG
AR | ESR1 | PGR | PPARG
AR | ESR1 | ESR2
AR | ESR1
AR | ESR2 | PGR
AR | ESR2 | NR3C1
AR | ESR2 | NR3C1 | PGR
AR | ESR2 | PPARA
AR | ESR2 | RXRA
AR | ESR1 | PGR | NR3C1
AR | ESR1 | PGR | PPARA
AR | ESR1 | PGR | RXRA
AR | PPARG
AR | PPARA | PPARG
AR | ESR2
AR
AR | NR3C1
AR | NR3C1 | PGR
AR | PGR
AR | PPARA
AR | ESR1 | ESR2 | RARA
AR | RARA
AR | ESR1 | PGR | KLF4
AR | ESR1 | ESR2 | KLF4
AR | KLF4
AR | ESR1 | PGR | TP53
AR | ESR1 | ESR2 | TP53
AR | TP53
FOXM1 | TPARG
FOXM1 | PPARA | PPARG
FOXM1 | FOXM1
ESR2 | FOXM1
FOXM1 | NR3C1
FOXM1 | NR3C1 | PGR
FOXM1 | PPARA
FOXM1 | RXRA
ESR1 | ESR2 | FOXM1
ESR1 | PGR | FOXM1
FOXM1 | RARA
FOXM1 | KLF4
FOXM1 | TP53
AR | ESR1 | PGR | FOXM1
AR | ESR1 | ESR2 | FOXM1
AR | FOXM1
PPARA | RELA
PPARG | PPARG | RELA
ESR2 | RELA
NR3C1
NR3C1 | RELA
NR3C1 | PGR | RELA
PGR | RELA
PPARA | RELA
ESR1 | ESR2 | RELA
ESR1 | RELA
ESR2 | RELA
RELA | TP53
KLF4 | RELA
AR | ESR1 | ESR2 | RELA
AR | RELA
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JUN | PPARA | PPARG
ESR2 | JUN
JUN
JUN | NR3C1
JUN | NR3C1 | PGR
JUN | PPARA
JUN | PGR
ESR1 | ESR2 | JUN
ESR1 | JUN | JUN
JUN | RARA
JUN | KLF4
AR | ESR1 | PGR | JUN
AR | ESR1 | ESR2 | JUN
AR | JUN
FOXM1 | JUN
FOXM1 | RELA
FOXM1 | JUN | NFKB1
JUN | RELA
JUN | NFKB1 | RELA
JUN | NFKB1
JUN | NFKB1 | RARA
JUN | NFKB1 | PPARA | PPARG
JUN | NFKB1 | NFKB1
JUN | NFKB1
JUN | NFKB1 | NR3C1
JUN | NFKB1 | NR3C1 | PGR
JUN | NFKB1 | PPARA
JUN | NFKB1 | RXRA
ESR1 | ESR2 | JUN | NFKB1
ESR1 | PGR | JUN | NFKB1
JUN | NFKB1 | TP53
JUN | ESR1 | JUN | JUN | NFKB1
AR | ESR1 | ESR2 | JUN | NFKB1
AR | JUN | NFKB1
reaction

Figure S2

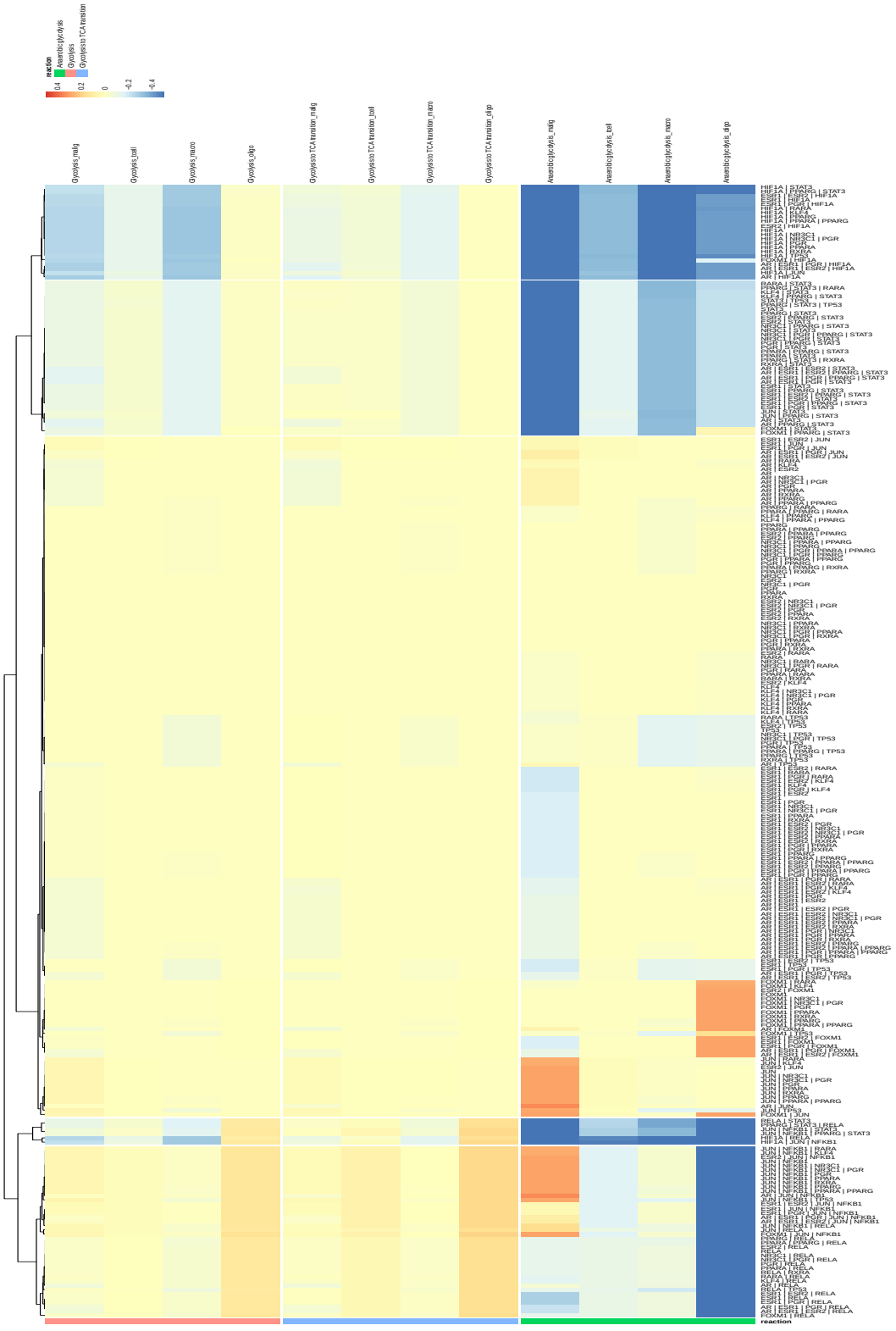
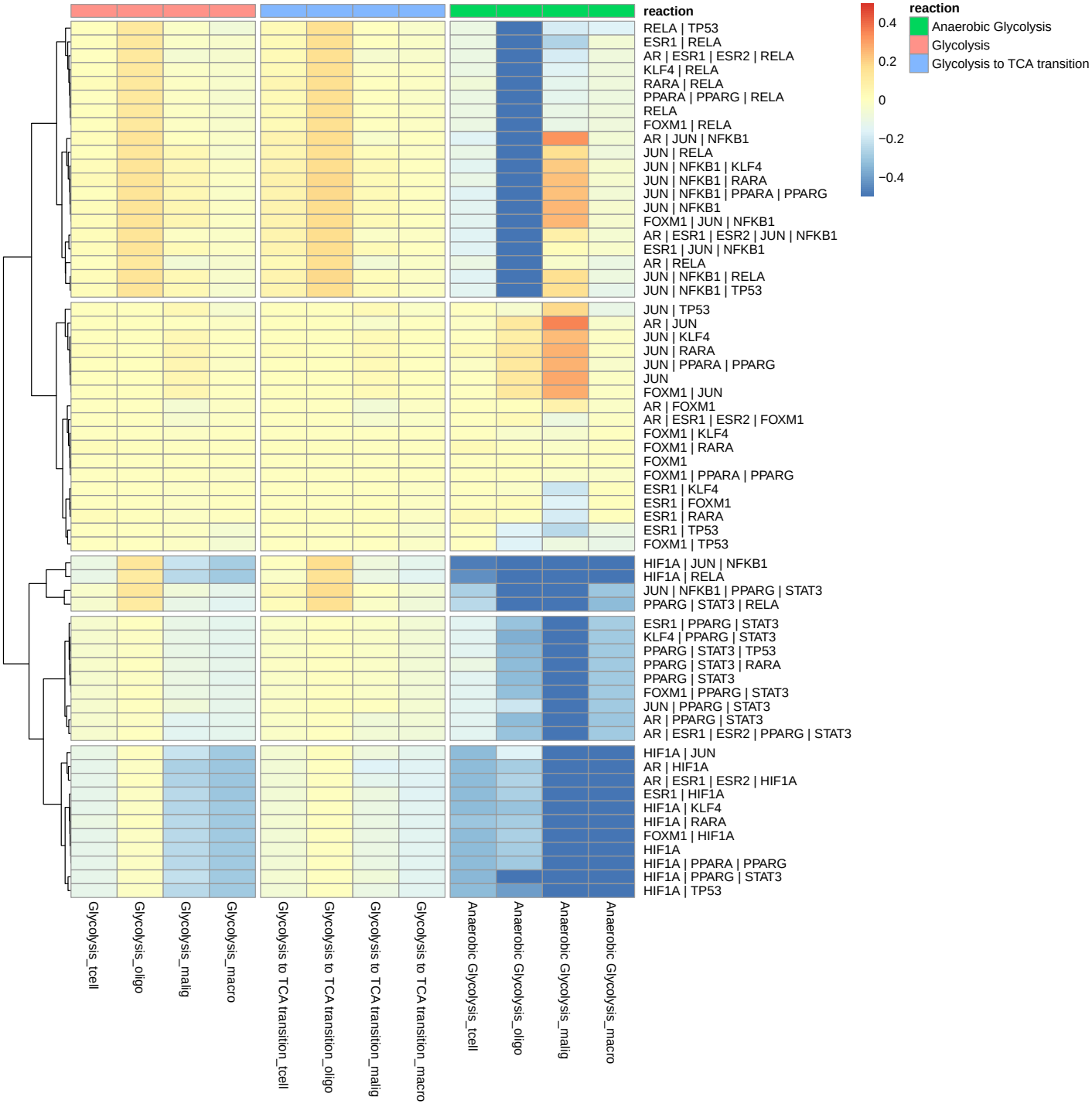

reaction
Anaerobicglycolysis
Glycolysis
Glycolysis to TCA transition
0.4
0.2
0
-0.2
-0.4
Glycolysis_mitq
Glycolysis_cyt
Glycolysis_macro
Glycolysis_dgp
Glycolysis to TCA transition_mitq
Glycolysis to TCA transition_cyt
Glycolysis to TCA transition_macro
Glycolysis to TCA transition_dgp
Anaerobicglycolysis_mitq
Anaerobicglycolysis_cyt
Anaerobicglycolysis_macro
Anaerobicglycolysis_dgp

Figure S3


reaction
RELA | TP53
ESR1 | RELA
AR | ESR1 | ESR2 | RELA
KLF4 | RELA
RARA | RELA
PPARA | PPARG | RELA
RELA
FOXM1 | RELA
AR | JUN | NFKB1
JUN | RELA
JUN | NFKB1 | KLF4
JUN | NFKB1 | RARA
JUN | NFKB1 | PPARA | PPARG
JUN | NFKB1
FOXM1 | JUN | NFKB1
AR | ESR1 | ESR2 | JUN | NFKB1
ESR1 | JUN | NFKB1
AR | RELA
JUN | NFKB1 | RELA
JUN | NFKB1 | TP53
JUN | TP53
AR | JUN
JUN | KLF4
JUN | RARA
JUN | PPARA | PPARG
JUN
FOXM1 | JUN
AR | FOXM1
AR | ESR1 | ESR2 | FOXM1
FOXM1 | KLF4
FOXM1 | RARA
FOXM1
FOXM1 | PPARA | PPARG
ESR1 | KLF4
ESR1 | FOXM1
ESR1 | RARA
ESR1 | TP53
FOXM1 | TP53
HIF1A | JUN | NFKB1
HIF1A | RELA
JUN | NFKB1 | PPARG | STAT3
PPARG | STAT3 | RELA
ESR1 | PPARG | STAT3
KLF4 | PPARG | STAT3
PPARG | STAT3 | TP53
PPARG | STAT3 | RARA
PPARG | STAT3
FOXM1 | PPARG | STAT3
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AR | ESR1 | ESR2 | HIF1A
ESR1 | HIF1A
HIF1A | KLF4
HIF1A | RARA
FOXM1 | HIF1A
HIF1A
HIF1A | PPARA | PPARG
HIF1A | PPARG | STAT3
HIF1A | TP53
Glycolysis_tcell
Glycolysis_oligo
Glycolysis_malig
Glycolysis_macro
Glycolysis to TCA transition_tcell
Glycolysis to TCA transition_oligo
Glycolysis to TCA transition_malig
Glycolysis to TCA transition_macro
Anaerobic Glycolysis_tcell
Anaerobic Glycolysis_oligo
Anaerobic Glycolysis_malig
Anaerobic Glycolysis_macro
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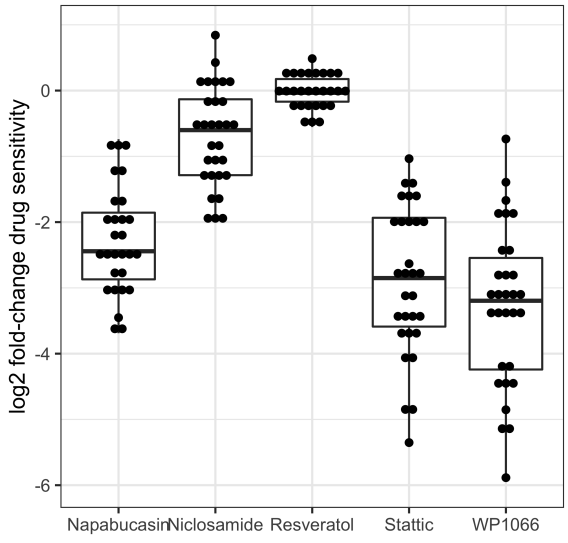
0.2
0
−0.2
−0.4
reaction
Anaerobic Glycolysis
Glycolysis
Glycolysis to TCA transition

Figure S4


log2 fold-change drug sensitivity
0
-2
-4
-6
Napabucasin
Niclosamide
Resveratol
Stattic
WP1066