Electronic Supplementary Material (ESI) for Integrative Biology.

Analysis with BioGRID

We queried the genes from our examples in the BioGRID database.

Among the list of interactions that appear for each query, we selected only "genetic interactions" and ignored the physical interactions in the database.

We searched for interactions with only the genes that appeared in our filtered (significant) genetic interaction networks.

For each queried gene, we cross-checked with our model. In blue, we show the link with the model whether the interaction was found or not.

In some cases, there was no overlap with the genes of our model. We listed them anyway when there were less than 10 genetic interactions identified in the BioGRID database.

For each of the genes we queried, there were few genetic interactions listed except for MYC gene where more than 100 genetic interactions exist.

1. *Restriction point model*

CDC20: Only genetic interaction is found: SIRT1 listed as negative genetic interaction

E2F1: 3 negative genetic interactions with HDAC2, HDAC3, and HDAC8.

CDKN1A (p21): one phenotypic enhancement is found with **CDKN1B (p27)**, one phenotypic suppression is identified with RNF114, and one synthetic rescue with TP63.
=> The genetic interaction between p21 and p27 does not appear in our analysis.

2. *Cell fate model*

XIAP: two phenotypic suppressions are found with CASP2 and with **CASP8**.
=> In the model, we found that overexpression of XIAP and overexpression of CASP8 lead to an epistatic interaction with respect to apoptosis in the TNF-activated signal.
XIAP overexpression (P1=0) suppresses the overexpression of CASP8 (P1=25). Indeed, the double mutant has a probability P12=0.

BCL2: one phenotypic suppression is found with CASP2, another one with **CASP8**, and a dosage rescue with ITLN1.
=> The genetic interaction between BCL2 and CASP8 does not appear in our analysis.

cFLIP: one phenotypic suppression with NOL3 is identified.

TNFR1: one phenotypic suppression with NOL3 is identified.

TNF: 7 genetic interactions are found:
- phenotypic suppression with CHUK, PSMD9, RAC1, and UBE2N
- negative genetic interaction with HDAC2
- phenotypic enhancement with HNRNPA1 and PSMD9

IKK1: one phenotypic suppression with **TNF** and another one with PSMD9 are identified.
=> In the model, we found that deletion of IKK1 and deletion of TNF lead to an epistatic interaction with respect to the necrosis phenotype in the TNF-activated signal (IKK deletion has no effect on loss of TNF), and overexpression of IKK1 and deletion of TNF lead to an epistatic interaction with respect to survival in the TNF-activated signal (TNF deletion has no effect on overexpression of IKK1).

3. *MAPK model*

AP1 and **JUN**: negative genetic interactions with HDAC1, HDAC2, HDAC4 and phenotypic enhancement with RELA and SENP2.

CREB: phenotypic enhancement with BRCA1 and positive genetic interaction with HDAC6.

ATM: phenotypic enhancement with **TP53**, POLQ, TERC
=> The genetic interaction between ATM and TP53 does not appear significantly in our analysis.

ERK (MAPK1): phenotypic enhancement with RPS6KA5

PTEN: negative interaction with HDAC4

MDM2: negative genetic interactions with HDAC1, HDAC2, and HDAC3; phenotypic suppression with KAT2B, **TP53**, and MTBP.
=> overexpression of TP53 and of MDM2 lead to a suppressive genetic interaction with respect to apoptosis in the model

MYC (c_Myc) is involved in 104 genetic interactions including dosage lethality (e.g., MAP2K3 (MEK3)), negative genetic interaction, phenotypic suppression and enhancement.

TP53: 19 genetic interactions identified with BioGRID including negative genetic interactions, phenotypic enhancement with **ATM,** phenotypic suppression (with **MDM2**), synthetic rescue with p63**,** and synthetic growth defect.
=> see above for TP53 and MDM2.
=> no significant genetic interaction was found between ATM and TP53 in the model

RAS (HRAS): negative genetic interaction (HDAC2, SIRT1, SIRT5) and phenotypic suppression with PLAU.

TAK1: phenotypic enhancement (TAB1), suppression (MYD88, TIRAP) and synthetic rescue (STE11)

EGFR: negative interaction with HDAC2

GADD45: negative (SIRT1, SIRT3) and positive (HDAC7) interactions

MEK1: phenotypic suppression with PLAU