Phenotype Switching during Tumor Necrosis Factor alpha Signaling

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Abstract

Tumor Necrosis Factor alpha (TNFα) is a pleiotropic cytokine involved in phenotypic decisions such as apoptotic/necrotic death, proliferation. Aberrant TNFα signaling is implicated in numerous pathological conditions. Designing therapeutic strategies to modulate these conditions require insights into the mechanisms governing context-specific phenotypic response to TNFα. Signal transduction culminating in such responses is orchestrated by underlying molecular network of nodes interconnected by edges. Using a comprehensive, well-annotated, manually curated TNF-α signaling network, we show that a graph-theory based dimensionality reduction via modularization can lead to functionally consistent, conserved modules in the network. We identify 19 candidates which when knocked down one-at-a-time significantly disturbs the network robustness yet preserves network modularity. Boolean dynamic simulations and attractor analysis of the underlying state transition graph show that targeting cIAP1/2 and MKRN1 can lead to reliable phenotype switching from proliferation to apoptosis. Knocking off BAX-BAK and LUBAC may result in switching from apoptosis to proliferation. These combinations causing phenotype switching could be potential targets for TNFα based therapeutic strategies.

Methodology

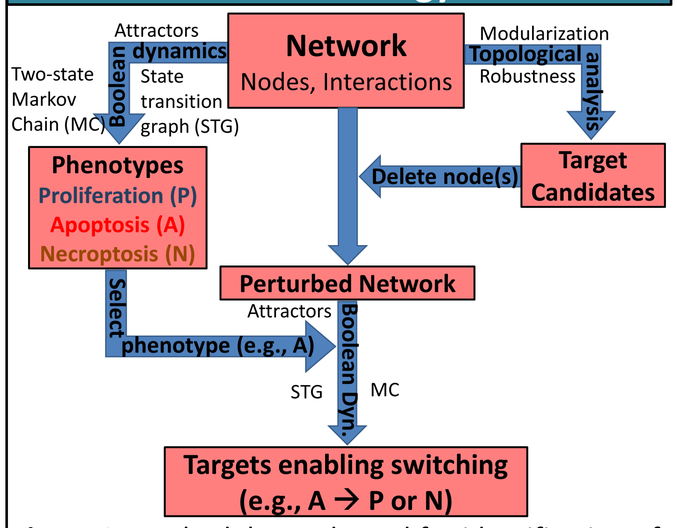

Figure 1: Methodology adopted for identification of targets that enable phenotype switching.

Network statistics

Attribute	Count
Nodes	423
Edges	341
Proteins	275
Genes+mRNA	62
Phenotypes	4
Primary Literature	663
Boolean rules (Logic)	284
Input + Housekeeping nodes	140
Fixed-point attractors	27

Manually curated TNFα Signaling Network

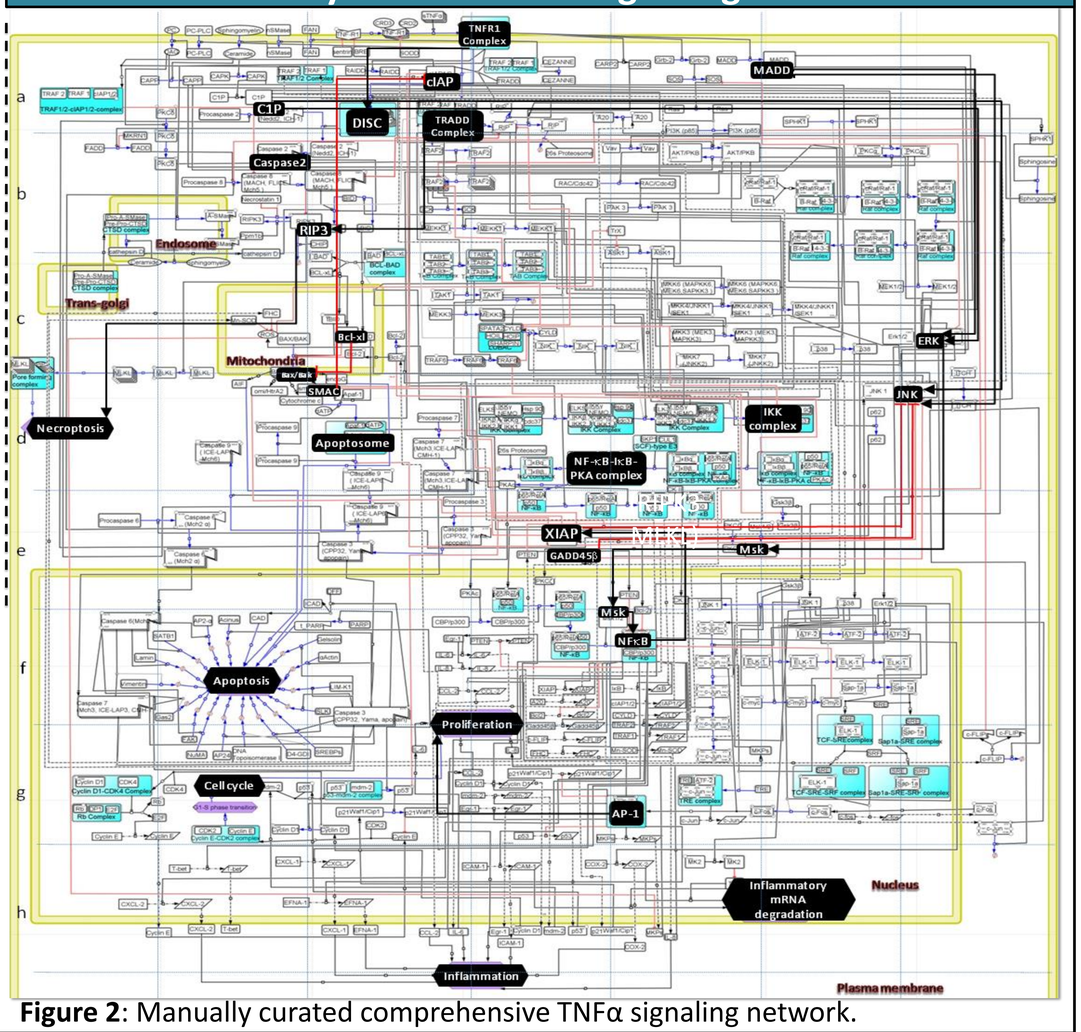

Figure 2: Manually curated comprehensive TNFα signaling network.

Target identification: Topological and fixed-point attractor analysis

Network consists of 24 functionally consistent modules

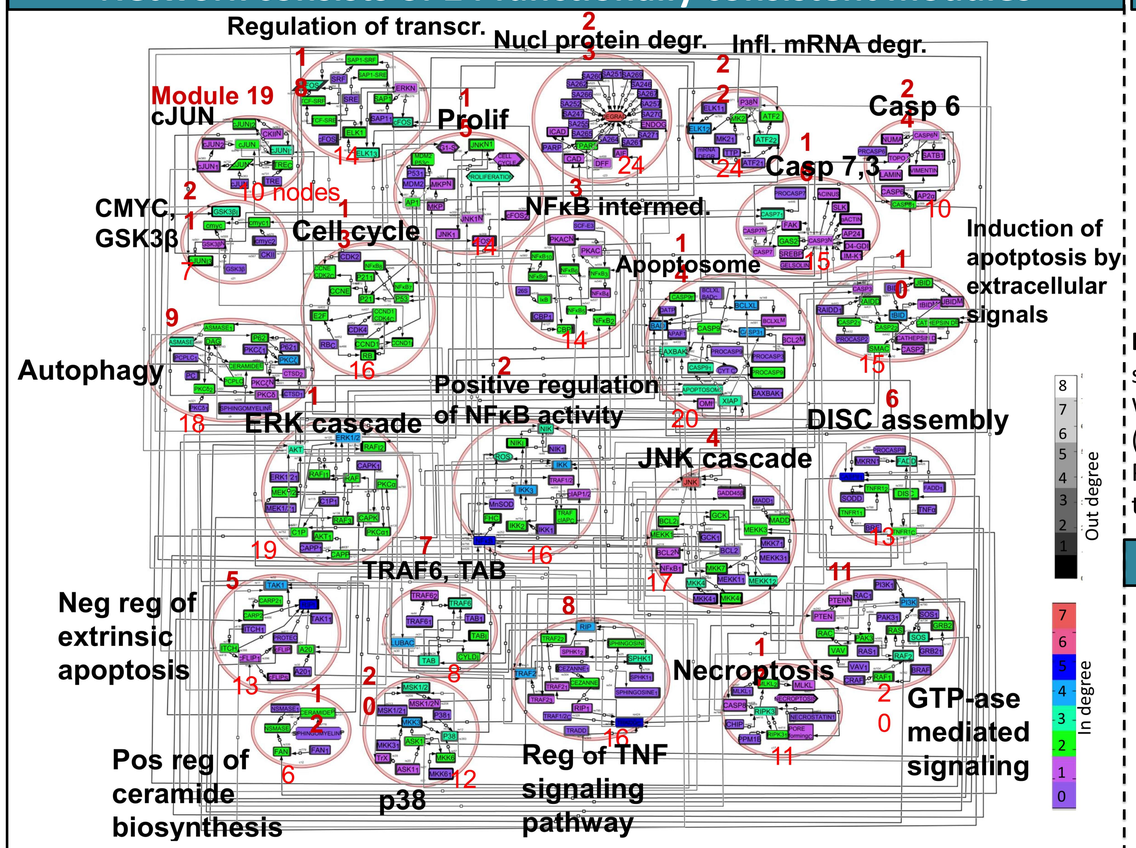

Figure 3: 24 functionally consistent modules. Function assigned using GO terms.[1] M=0.85

Phenotype probability

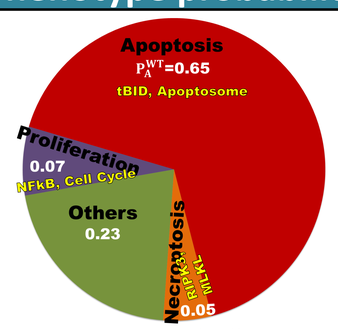

Figure 4: Probability (P^{wt}) of network settling into a certain phenotype. WT refers to the original (unperturbed) network in Figure 2. Probabilities were estimated using two-state Markov model.[4,5]

Target candidates

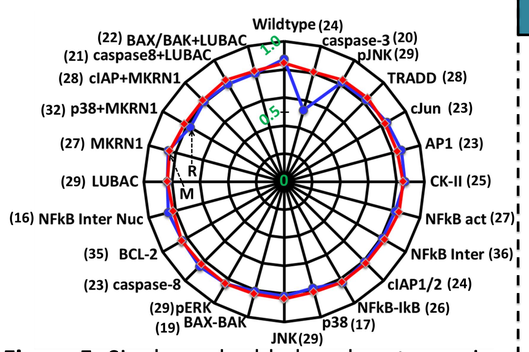

Figure 5: Single or double knock-outs causing reduction in both network modularity (M) and robustness (R). Number next to a candidate within bracket is the number of modules obtained after knock-out.

Phenotype Switching

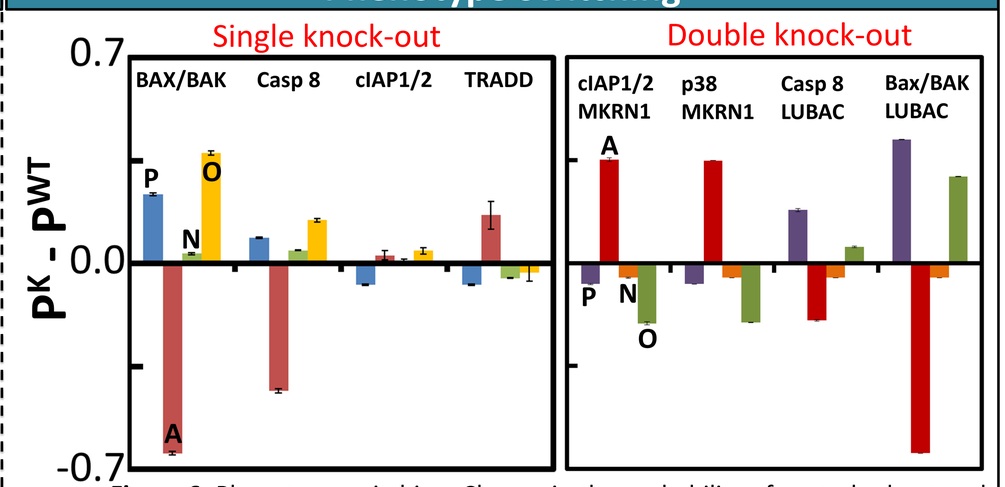

Figure 6: Phenotype switching: Change in the probability of perturbed network settling into a phenotype reflecting the switching caused by the perturbation via single/double knock-out.

Modularity and Robustness

Modularity (M) is the fraction of weighted directed edges between nodes in a module vs expected fraction if randomly connected.[2] Range for M is [0,1]

Robustness (R) is the persistence of the network's characteristic behavior under perturbations.[3] Range for R is [0, 1]

Conclusions

- Well annotated TNFα signaling network
- Network predicts that apoptosis (P^{WT} = 0.65) is more likely
- Novel approach for target identification
- cIAP1/2 & MKRN1: Combination target for switching proliferation to apoptosis phenotype.
- BAX-BAK & LUBAC: Combination target for switching apoptosis to proliferation phenotype.

References

1. Huang *et al*. (2008), Nature Prot.
2. Newman (2011), Nature Physics
3. Stelling *et al*. (2004), Cell
4. Davidich *et al* (2013), PLoS One
5. Saadatpour and Albert (2013), Methods

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