Phenotype Switching during TNFα-TNFR1 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 TNFα-TNFR1 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 20 candidates which when knocked down one-at-a-time preserves the network's modularity as well as robustness. Moreover, using information from databases, we further identify cell-type specific interactions in the network. Boolean dynamic simulations of this complex system and attractor analysis of the underlying state transition graph show that targeting BCL-2 and ERK-1/2 can lead to reliable phenotype switching from proliferation to apoptosis. While, knocking-off JNK-1 with LUBAC can result in switching from apoptosis to proliferation. Analysis of tissue-specific network, generated by incorporating the relevant constituent state information, led to prediction of the fraction of an ensemble of cells of MCF7 (breast cancer) and U937 (lymphoma) exhibiting the three distinct phenotypes. These combinations causing phenotype switching maybe considered potential targets for TNFα based therapeutic strategies.

Work Flow

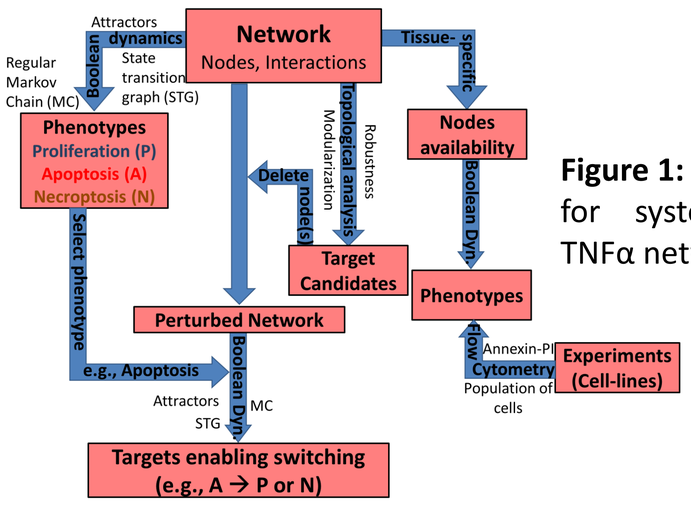
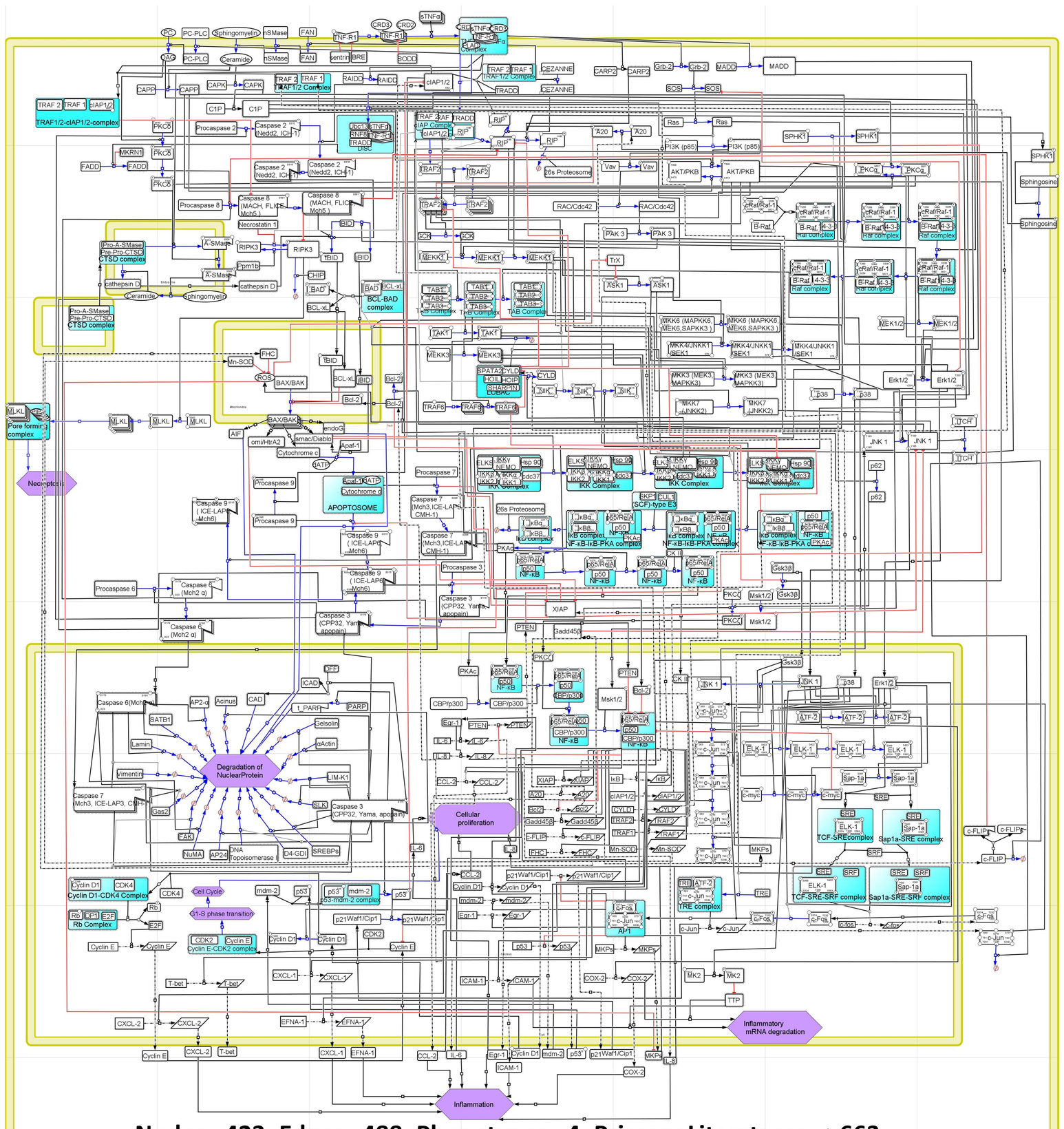


Figure 1: Work flow adapted for systemic analysis of TNFα network

Manually curated TNFα-TNFR1 Signaling Network



Topological analysis

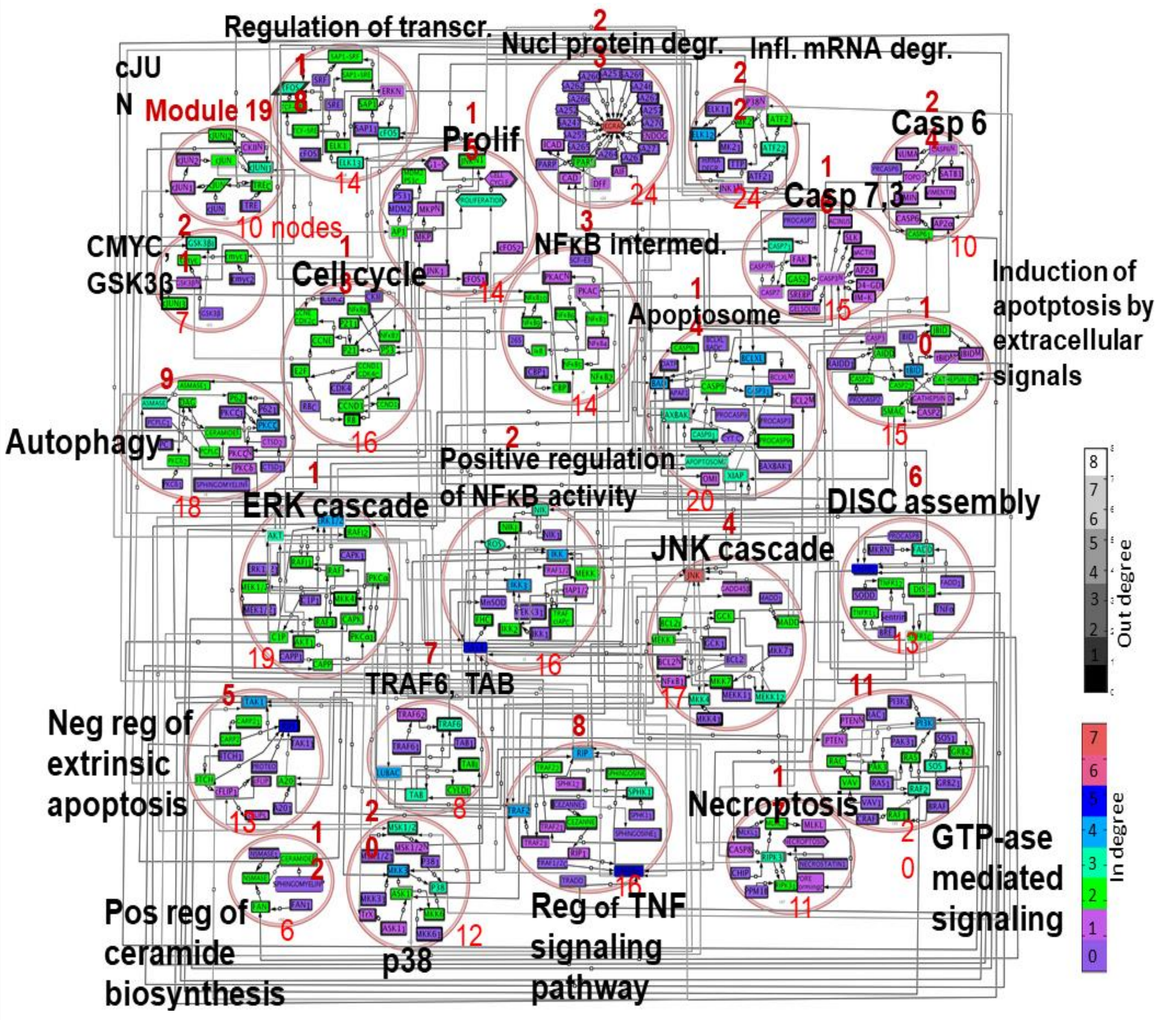


Figure 2: 24 functionally consistent modules. Function assigned using GO terms.[3] M=0.85 & R=0.87

Dynamic analysis

Phenotype Probability

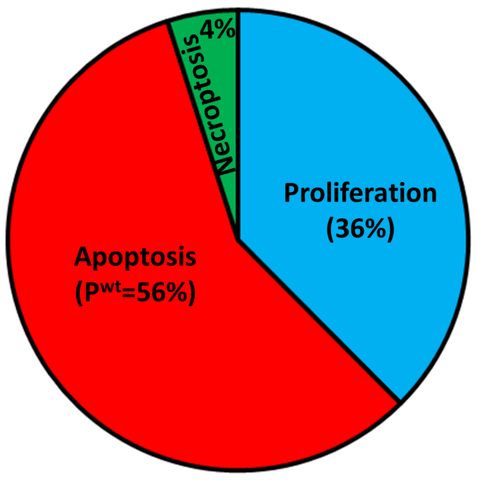


Figure 3: Probability (P^{wt}) of network settling into a certain phenotype. wt refers to the original (unperturbed) network in Figure 1. Probabilities were estimated using regular Markov model.[4,5]

Phenotype Switching

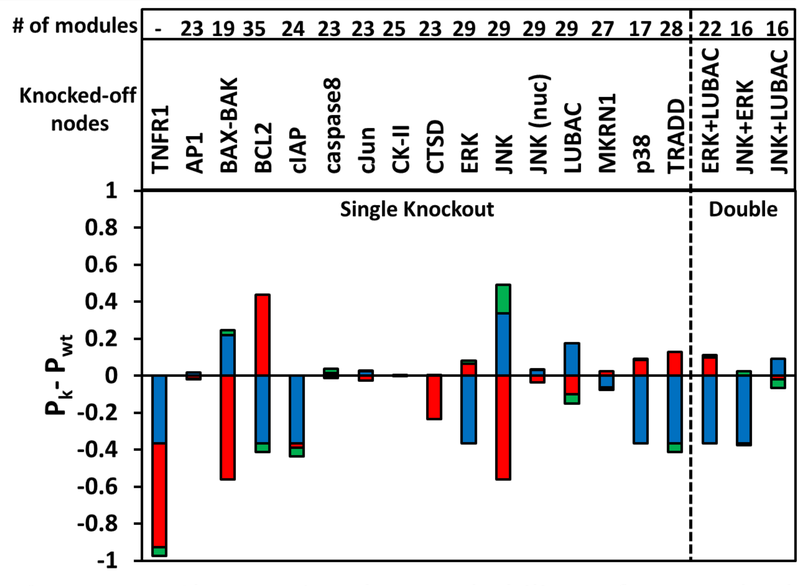


Figure 4: Change in the probability of perturbed network settling into a phenotype reflecting the switching caused by the perturbation via single/double knock-out while preserving the change in the modularity and robustness within the range of ±8%.

Tissue-specific Phenotype Prediction

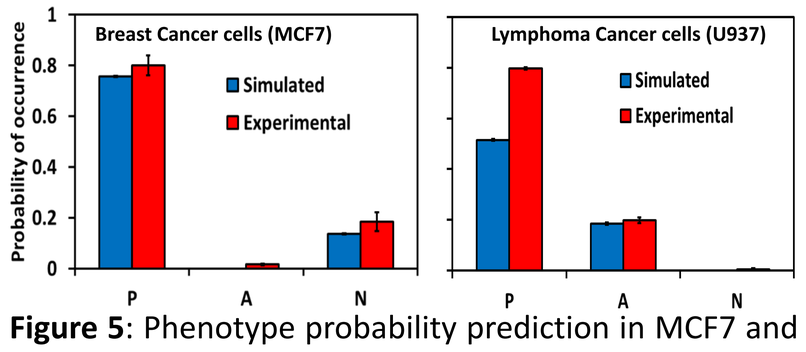


Figure 5: Phenotype probability prediction in MCF7 and U937 cell lines using Boolean dynamic simulations of tissue-specific network. Tissue-specific information taken from celllinenavigator[6] and probabilities calculated in expt. using Annexin-PI.

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
6. medicalgenomics.org/celllinenavigator

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Conclusions

- Well annotated TNFα signaling network
- Network predicts that apoptosis (P^{WT} = 0.56) is more likely
- Novel approach for target identification
- BCL2, ERK-1/2, p38 & TRADD: targets for switching P to A
- JNK-1, LUBAC, Bax-Bak: targets for switching A to P.
- LUBAC combination with JNK & ERK: switch A-P & P-A respectively
- Tissue-specific network predicts probable occurrence of phenotypes