Probing apoptosis dynamics at the receptor level

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***Short Abstract* — Among the cells that undergo apoptosis upon TRAIL treatment, there is a dramatic cell-to-cell variability in the timing of activation of the initiator caspases. This variability in cell response to death ligands currently in clinical trials such as TRAIL, DR4 or DR5 agonistic antibodies, might help elucidate the patient-specific nature of targeted therapy outcome. In the present study, we focused on the Death receptor Induced Signaling Complex (DISC) subsystem of the apoptosis network, to understand its dynamics and impact on other modules of the pathway (the mitochondria and the effectors caspases with their regulators) and on cell death. Using pySB, a rules-based programmatic approach, we investigated how DISC dynamics alone inform on sensitive modules within the whole apoptosis network that would indicate targets for co-treatment.**

***Keywords* — Apoptosis, death-induced signaling complex, TRAIL, death receptor, caspase, rules-based modeling.**

I. Background

WE have shown that TRAIL induces cell death in only a subset of cells of a clonal population as a result of pre-existing variability in the concentrations of apoptotic regulators [1,2]. There has been extensive research dedicated to identifying predictive biomarkers of tumor sensitivity to TRAIL and other ligand-based therapies. Although some biomarkers have emerged [3-6], there is still no comprehensive understanding that unifies the observed tumor cell type-specific behaviors, in particular differential responses to anti-cancer drugs. The collective realization is that no single protein measurement is predictive of therapeutic outcome. Large-scale studies focusing on multiple genetic biomarkers may be partially inadequate given the observed fractional killing of genetically identical clonal cell populations. We coupled live cell imaging and quantitative biochemical analyses with theoretical and computational methods to provide a global understanding of the origins of tumor cell heterogeneity in response to anti-cancer drugs. Ultimately this should help identify, on a tumor cell type basis, the most predictive set of biomarkers and design optimal therapeutic combinations.

Acknowledgements: This work was funded by NIH grant P01 CA139980.

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II. Aims

A. Quantitative biochemical measurements of DISC to Mitochondria network.

We hypothesized that the dynamics of the death receptor-mediated reactions induced by ligand-based cancer therapies reveal sensitive parameters of the whole apoptotic network specific to a tumor cell type. Here we collected and assembled a comprehensive multi-dimensional data set that characterizes the DISC-to-Mitochondria network at the single cell level across multiple tumor-cell types using quantitative biochemistry and dynamic live-cell imaging, in multiple tumor cell lines.

B. Modeling and network analysis of death ligand-induced apoptosis.

It is well accepted that the dependency of tumor cell sensitivity to cellular components is multifactorial. Using a novel rules-based modeling approach to integrate large scale profiling datasets with more in-depth mechanistic studies we developed a detailed reaction model of death-ligand induced apoptosis to explore the DISC-to-Mitochondria network and identify sensitive modules within the whole apoptosis pathway that would be targets for co-treatment.

III. Conclusion

Here we showed how death ligands in clinical trials affect the DISC dynamics, and what we can learn on the state of the cell using computable models, which might help identify anti-cancer drug co-target modules.

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