How Cells Decide Between Apoptosis and Survival in Response to DNA Damage

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***Short Abstract* — In response to DNA damage eukaryotic cells arrest their cell cycle and then either repair the damage and proliferate or cease to proliferate and apoptose or senesce. We are intrested in understanding how cells compute their fate in response to varying types and degrees of DNA damage. To do so we are quantitatively monitoring DNA damage signaling, the cell cycle machinery, the apoptotic machinery as well as mitogen/stress activated kinase pathways. These data will form the basis of models that will seek to characterize the cellular decision process in response to DNA damage.**

***Keywords* — DNA damage, Signal Transduction, Cell Decision Process, Principal Component Analysis, Partial Least Square Regression, ODE modeling**

I. BACKGROUND

The accumulation of DNA damaged cells in multi-cellular organisms can be avoided by the efficient repair of DNA damage, by the activation of cell cycle checkpoints that provide time for DNA repair, and by the elimination of damaged cells by apoptosis. The DNA damage signaling network can be thought of as a computational device in which the input is the extent of the DNA damage and the output is repair, cell cycle arrest and repair, or cell death. These cellular decisions are made by a signaling network of protein kinases, but exactly how the cell commits to these very different outcomes is unclear. The goal of this project is to generate a quantitative, network level understanding of how this cellular decision process works through the synergistic application of experimental and computational methods. This project builds upon the work of Lauffenburger, Yaffe and co-workers who successfully monitored and modeled the activity of pro-death and pro-survival signal transduction pathways in response to EGF, insulin and TNFα [1,2]. As was the case for the cytokine induced apoptotic decision, apoptosis will be induced by a combination of chemotherapeutic induced DNA damage in combination with cytokine treatments to drive populations of cells to differennt levels of apoptosis. Both the cellular outcome and the intracellular signaling networks will be monitored experimentally. Subsequently, modeling methods will be used to characterize how the signal transduction networks calculated the cell fate.

II. RESULTS

In the past year we have assembled the molecular toolkit necessary to monitor the intracellular information processing that results in cell survival or death. We are now capable of monitoring the activities of nine kinases essential to the DNA damage response. In addition, we can monitor the protein levels and phosphorylation states of ~30 DNA damage response, cell cycle regulatory and cell death regulatory proteins. The intracellular signaling measurements and the cellular outcomes were selected because they provide a broad overview of the multiple regulatory pathways that are likely to be affected by the DNA damage response, including progression through various stages of the cell cycle, cell cycle arrest, initiation of DNA repair, survival and stress responses, chromatin remodeling and transcriptional regulation. Our dense sampling of these activities is expected to provide a systems-level view of the state of the cell as a function of time after DNA damage.

We have embarked on a multi-month long data collection process in which we will correlate measurements of intracellular signaling with measurements of cellular outcome (i.e. survival or apoptosis. These data sets will be merged and used to generate predictive mathematical models of the cellular decision process. The models will be rigorously tested for their accuracy and predictive power by monitoring the effects of quantitative perturbations to the signaling network. Through the iterative application of experiment and modeling we will build upon the notable progress in this field and develop a network level understanding of DNA damage response signaling that we believe will suggest means for improving the prevention and treatment of cancer.

REFERENCES

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Acknowledgements: This work was funded by NIH grant U54 CA112967. GJO was funded by American Cancer Society Grant #PF-06-094-01-CCG.

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