How Cells Decide Between Apoptosis and Permanent Arrest 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, enter a state of permanent arrest (senescence) or apoptose. We are intrested in understanding how cells compute their fate in response to varying types and degrees of DNA damage. To do so we have quantitatively monitored cellular outcomes in response to DNA damage and in parallel the DNA damage signaling pathways, the cell cycle machinery, the apoptotic machinery and the mitogen/stress activated kinase pathways. We are now using Principle Component Analysis and various regression methodologies to probe these large cellular response and signaling data sets for information processing events that 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**

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 type and extent of the DNA damage and the output is cell cycle arrest and repair, permanent cell cycle arrest or cell death. A signaling network consisting of protein kinases makes these cellular decisions, 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]. As was the case for the cytokine induced apoptotic decision, cellular signaling space has been probed using a combination of cues. In this case apoptosis has been induced by chemotherapeutic induced DNA damage in combination with cytokine treatments to drive populations of cells to different levels of apoptosis. Both the cellular outcome and the intracellular signaling networks have been monitored experimentally. Currently, principle componant analysis and partial least square regression is being used to characterize how the signal transduction networks calculated the cell fate.

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II. RESULTS

In the past year we have monitored the cellular response of the U2-OS osteosarcoma cell line to doxorubicin treatment in combination with TNFα treatement and the signaling events underlying these responses. We quantitatively measured the proliferation, cell cycle arrest kinetics and apoptosis levels. For the signaling measurements we directly measured the activities of six kinases essential to the DNA damage response including Akt, Erk, Jnk, MK2, Chk1 and Chk2. In addition, we monitored 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.

With these cellular response and signaling data sets in hand we have now started the process of modeling this data with the goal of correlating intracellular signaling events with cellular outcome (i.e. survival, arrest or apoptosis). The resulting 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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