



SYSTEMS BIOLOGY OF THE DNA DAMAGE RESPONSE: IMPLICATIONS FOR RATIONAL DESIGN OF CANCER THERAPY

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Intentional creation of DNA damage constitutes one of the mainstays of modern cancer therapy. In response to genotoxic damage cells activate a complex multi-pathway kinase signaling network that mediates cell cycle arrest, DNA repair, cell cycle re-entry, cell death, or senescence. Exactly how these signals are integrated at the molecular level remains poorly understood. Our laboratory has been using structural, biochemical, cell biological/RNAi, and computational approaches to measure and model the activities of signaling pathways in response to DNA double strand breaks (DSBs) with the goal of understanding how cells process these signals to make and execute binary cell fate decisions such as life or death.

In this talk I will discuss our recent work examining the interconnections between signaling modules controlling genomic integrity, cell cycle progression, survival, apoptosis, and stress signaling in U2OS cells exposed to doxorubicin and the cytokine $TNF\alpha$. We gathered a quantitative dataset of 3500 signaling measurements of 17 molecular signals, and 500 phenotypic responses of cell cycle progression and cell death, and used mathematical modeling approaches to systematically discover signal-response relationships within the DSB-responsive protein signaling network. PCA-PLSR approaches revealed important signals emerging from the p38-MK2 and ATM networks that control cell cycle arrest and survival in a p53-dependent manner. These relationships were then verified in murine models and human clinical studies. Implementation of a new computational approach, stepwise regression, has now revealed paradoxical and unexpected roles for the MAPK pathway in controlling S-phase entry and survival after DNA damage, along with integration of MAPK and $NF\kappa B$ signals as key determinants of cellular response. These findings have important implications for the improvement of existing combination and targeted chemotherapeutics, and for the development of novel targeted personalized therapies.