Dynamics analysis of apoptosis network

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***Short Abstract* — resisting cell death is one of the hallmarks of cancer. To investigate the dysregulation of apoptosis associated with cancer, we developed a mathematical model of mitochondrial apoptosis induced by intrinsic and extrinsic signals. Bifurcation analysis and multiparameter sensitivity analysis was used to study the network dynamic properties. Model-based parameter sensitivity analysis uncovered a system-level process that contributes to apoptosis resistance due to mutations in cancer cells, and the predicted behavior was supported by our MD and MMGBSA calculation. The results helped build a solid bridge between biological function and regulatory network dynamic properties, which further uncovered the mechanism of mutation-dependent carcinogenesis.**

***Keywords* — mitochondrial apoptosis pathway, mathematical model, bifurcation analysis, multiparameter sensitivity analysis, oncogenic mutation, MD and MMGBSA .**

I. Background

All cancers are mainly caused by somatic mutations [1]. However, systematically understanding of the mechanism and correlation between mutation and oncogenesis is limited. The discovery that oncogenic mutations are concentrated in a few core biological functional pathways [2-3] indicated oncogenic mechanisms are highly related to the dynamics of biologic regulatory networks, which govern the pathway behavior [4].

Resisting cell death is one of the hallmarks of cancer and apoptosis pathway is a mutation-rich pathway [5]. The study of network properties of apoptosis pathway may contribute to uncover a tip of the mechanism of carcinogenesis due to mutations.

II. Preparation of Abstracts

To investigate the dysregulation of apoptosis associated with cancer, we developed a mathematical model of mitochondrial apoptosis induced by intrinsic and extrinsic signals. The regulatory network was mainly focused on the mitochondrial outer membrane (MOM) events concerned with Bcl-2 protein family. Ordinary equations (ODE) were used to describe the network and simulate its dynamic properties. Model-based bifurcation analysis indicated that the life to death switch can be illustrated by a sudden irreversible increase of bax oligomer concentration when stimulus (apoptotic signal) crosses a certain point, which is called saddle-node bifurcation. Multiparameter sensitivity analysis has highlighted some sensitive parameters whose perturbation significantly affects the bifurcation point and thus the output of the system, which may lead to cancer. Based on our model, we predicted that the protein interaction domains related to the sensitive parameters are supposed to be enriched with more mutations. To test our prediction, we first collected the mutations occurred in tumor phenotype from COSMIC mutation database, and then mapped them to protein domains involved in our network. Good correlation was found between sensitivity spectrum and domain mutation enrichment spectrum that most of the sensitive the parameter to the bifurcation point correspond to high domain mutation enrichment. We further supposed that it is those mutations that cause the changes of the sensitivity parameters and the subsequent instability of the network by alternating the binding energy of corresponding protein interaction that contribute to carcinogenic process. Using MD and MMGBSA algorithm, we then calculated the binding energy change between wild type and mutant protein complex in our model. We surprisingly found that indeed 80% of the mutations in domains related to sensitive parameters have changed the binding energy to oncogenic direction corresponding sensitivity analysis prediction, while mutations in domains that have not been highlighted have on coincident affection. Further more, we also test SNP enrichment and the effect of energy change in associated domains for comparison and found no significant difference between dominant interactions and other interactions.

III. Conclusion

By analysis the model systematically, we have built a solid bridge between biological function and regulatory network dynamic properties in apoptosis pathway and conclude that mutations contribute to resisting cell death mainly through disturbing the dominant interactions in the network which might lead to cancer.

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